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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 :
G01N 21/90, H04N 7/18
G12B 5/00, B23Q 16/02

A1

(11) International Publication Number: WO 90/02326

(43) International Publication Date: 8 March 1990 (08.03.90)

(21) International Application Number: PCT/AU89/00312

(22) International Filing Date: 24 July 1989 (24.07.89)

(30) Priority data:
PJ 0002/88 23 August 1988 (23.08.88) AU
PI 9998/88 23 August 1988 (23.08.88) AU

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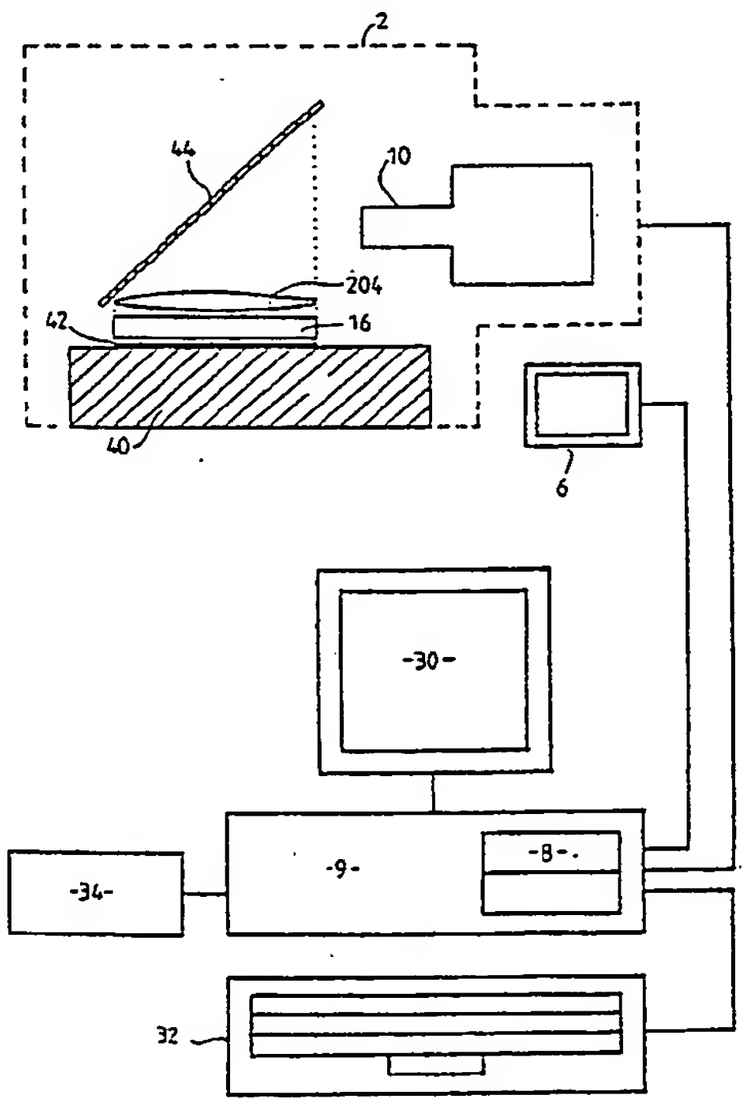
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: OPTICAL FLUID ANALYSIS IMAGING AND POSITIONING

(57) Abstract

Apparatus for use in optical analysis of sample arrays comprises a video camera (10) which provides a video signal to a personal computer (9) and display apparatus (6), (30). An image of the sample array is stored in pixels and can be displayed in real time or can be manipulated by means of the personal computer (9), for instance by overlaying different images. The camera (10) is mounted parallel to a sample plate (16), for compactness, a mirror plate (44) being used to allow the camera (10) to view the sample array. The camera (10) has a relatively short focal length and correcting means (204) are provided to correct marginal defects of the image. Sample plates (16) are positioned with respect to the camera (10) by means of a locking mechanism (326). The apparatus finds particular application in optical analysis of fluid medical samples.



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OPTICAL FLUID ANALYSIS IMAGING AND POSITIONING

The present invention relates to an apparatus for use in analysing a plurality of fluid samples.

To determine whether a fluid sample, such as a blood sample, has a particular characteristic, an appropriate reagent may be applied to the sample and then the sample examined by passing light therethrough or reflecting light from the surface thereof. For instance, it may be possible to detect a colour change in a sample. Alternatively in an agglutination test, particles are produced in a fluid sample and can be assessed in terms of quantity, or the presence of a particular pattern. In a known blood agglutination test for the presence of the AIDS virus, transmitted light is used in assessing the

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effect of an added reagent on a blood sample. Evaluation processes of the above type are normally carried out using a single light source and optical detector, and samples are illuminated one at a time. Usually at least one reference sample having the appropriate reagent applied thereto is also illuminated. Optical density readings for each sample are obtained from the signals generated by the optical detector on receipt of the light transmitted by the illuminated samples. The readings are derived on the basis of the levels of the signals. Comparing readings for test samples with readings for reference samples enables a decision to be made as to whether a test sample includes the characteristic for which the samples have been evaluated.

A number of apparatuses have been configured to implement the above evaluation process but each apparatus has at least one of the following disadvantages. As one detector is employed to receive the light from one sample at a time, all of the samples, including the reference samples, must be moved sequentially in the vicinity of the optical detector which is an extremely time consuming process. An apparatus disclosed in U.S. Patent No. 4,684,244 does move a plurality of samples with respect to an optical detector so that the detector effectively performs a raster scan of the samples but, like a number of the known apparatuses, the mechanism required to move the samples with respect to the detector is elaborate, complex and relatively cumbersome. The evaluation process also is susceptible to human error, whether it be in relation to placement of the samples in the apparatus,

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recordal of the readings, operation of the apparatus, including any set-up procedures, or entering the readings into a processing device. Known devices also limit a user with respect to the extent of evaluations which can be performed on a sample.

Further constraints include the fact that it is important that samples can be evaluated quickly. A commercial medical laboratory for instance might wish to evaluate several thousands of samples per hour. However, it can be extremely important that the evaluation should be carried out accurately. Visual inspection of samples with known apparatus for testing blood samples theoretically allows the inspection of for instance about 60,000 samples per hour. Automation of the evaluation process might significantly increase the throughput of samples. However, for automated evaluation equipment to be accepted generally, particularly where medical diagnostic samples are concerned and in developed countries, it must also meet a criterion of accuracy which is at least equal to the accuracy of non-automated visual inspection.

Hence, it is desirable to provide an apparatus for use in analysing fluid samples that is relatively simple in construction and operation, minimises the degree of human error involved in performing an evaluation process and provides some flexibility with respect to the evaluations which can be performed. Further, it is desirable that the apparatus should perform the evaluation process quickly while producing highly accurate results.

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An object of the present invention is to provide an apparatus for such a use which has at least one of these desirable attributes.

In accordance with the present invention there is provided apparatus for use in analysing a plurality of blood samples comprising:

means for illuminating a device, which device includes a plurality of receptacles arranged in an array, each receptacle having a sample disposed therein, so as to pass light through or reflect light from said receptacles;

camera means responsive to said light passed through or reflected from said receptacles for generating a video signal representative of the intensity of light passed through or reflected from the receptacles; and

processing means for processing said video signal, deriving from said video signal an array of pixels representative of said intensity at a predetermined instant, storing said array of pixels and processing stored pixels to determine if said samples have a determined characteristic.

Preferably said apparatus includes means for receiving said device.

Preferably said samples include at least one reference sample and said processing means uses at least one pixel corresponding to said at least one reference sample to derive a reference value and the existence of said predetermined characteristic for each sample is determined by comparing said reference value with a value derived for the sample from at

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least one pixel corresponding thereto.

Preferably said processing means is adapted to use said value for the samples to drive a colour display means, wherein a colour displayed to represent a sample is selected on the basis of whether the corresponding value lies in a range which corresponds to said colour.

Said processing means may also or alternatively be adapted to use said stored array of pixels to drive said colour display means. This allows manipulation of an image displayed on the display means for instance for further analysis, or comparison with pixels stored in relation to different samples. This can be particularly useful with certain types of sample for instance wherein the rate of change of a particular feature or features is significant, or where a predetermined characteristic is only temporarily present to be analysed.

Preferably said apparatus comprises a sampling unit which includes said receiving means, said illuminating means, said camera means, said processing means, and a display means which can be driven in real time by said video signal, or substantially in real time by said array of pixels.

Preferably an input interface and said colour display means are connected, in use, to said sampling unit.

Preferably said apparatus is able to

evaluate said samples to determine the presence of a number of predetermined characteristics. Available evaluations would include tests for the AIDS and hepatitis viruses, and an agglutination test to determine blood group and type of a blood sample.

Preferably said receiving means includes a movable support tray which can be positioned to extend from said sampling unit in a sample loading position and then be retracted to a sample scanning position. Preferably said illuminating means comprises an electroluminescent panel positioned underneath said device when said support tray is retracted. Preferably said device is a plate and said camera means is a CCD camera.

A preferred embodiment of the present invention will now be described, by way of example only, with reference to the accompanying drawings, wherein:

Figure 1 is a perspective view of a preferred embodiment of an apparatus for use in analysing a plurality of blood samples;

Figure 2 is a perspective view of part of the apparatus of Figure 1, shown in a loading position;

Figure 3 is a front view of the apparatus of Figure 2;

Figure 4 is a side view of the apparatus of Figure 2;

Figure 5 is a schematic diagram of a preferred embodiment of an apparatus for analysing a plurality of blood samples;

Figure 6 shows a part of the apparatus shown

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in Figure 5, in more detail;

Figure 7 shows a plan view of a lens for use in the apparatus shown in Figure 6;

Figure 8 is a plan view of a sample plate;

Figures 9, 10 and 11 illustrate a flow diagram of software employed in the apparatus of Figure 1;

Figure 12 shows a perspective view of part of a loading mechanism for use in the apparatus of Figure 1.

Figures 13a to 13c show plan views of the loading mechanism of Figure 11 in different stages of a loading process;

Figure 14 shows a plan view of the loading mechanism of Figure 12 after operation of a manual override; and

Figure 15 shows schematically an arrangement for displaying real-time and stored images in use of the appratus of Figure 1.

An apparatus for use in analysing a plurality of blood samples, as shown in Figures 1 to 4, can be considered as comprising four primary modules:

i) a sampling unit 2 providing the main mechanical apparatus;

ii) a personal computer 9 for results analysis;

iii) control circuitry comprising a logic unit for controlling mechanical operations of the sampling unit 2 such as loading and lighting; and

iv) display equipment comprising a monitor 6 and a computer screen 30.

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These modules are independent in that they can be replaced or removed for maintenance as separate items.

The sampling unit 2 includes a moveable support tray 4, a floppy disk drive 8 and lighting equipment. It also houses the monitor 6, the control circuitry, hard disc storage, and a CCD monochrome video camera 10 provided with a 12 to 16 mm lens for scanning the samples. The control circuitry is based on microprocessor technology, incorporating for instance INTEL 80286 and 80287 processors. The personal computer 9 receives signals output by the video camera 10, and deals with storage, analysis and display of these signals. Samples are loaded in the unit 2 by means of a servo drive mechanism which is also housed within the sampling unit 2 and is used to effect movement of the support tray 4 so that it can be extended and retracted with respect to the sampling unit 2, between loading and scanning positions respectively. Images obtained by means of the camera 10 may be displayed either on the monitor 6 or on the screen 30 associated with the computer 9, and may be real-time images or images stored and processed by means of the personal computer 9.

The sampling unit 2 optionally has additional ports associated with it, for instance a parallel port for connection to a hard copy printer (not shown), or a serial port for connecting additional modems. This can allow connection of the unit 2 to a network or a mainframe computer.

The servo drive mechanism and the support tray 4 are configured so that the support tray 4 is moved with respect to the sampling unit 2 in substantially the same manner as compact disc support trays are moved relative to respective compact disc players. This allows a sample plate 16 to be loaded into the unit 2 for inspection and analysis. However, the action of the drive mechanism is ramped so as to avoid sudden acceleration or deceleration of the tray 4 at either end of its travel. This is to avoid disturbance of samples being loaded into the unit 2. Further, the loading and scanning positions of the tray 4, at either end of its travel, are detected and controlled by means of optical switches. These have advantages with respect to mechanical switches in that the effects of bounce, wear, and mechanical design inaccuracies are substantially eliminated.

Referring to Figures 2, 4 and 8, the servo drive mechanism is able to cause the support tray to protrude from an opening 12 in the lower part of the sampling unit 2 and in the loading position 14, a sample plate 16 may be placed on the support tray 4. A sample plate 16 of the type which the support tray 4 is adapted to receive is relatively small, about 85.5 cm x 127.5 cm, and includes an array of 96 sample wells or receptacles 18. The wells 18 are arranged in eight rows and twelve columns with each well 18 having a diameter of about 6.5 mm. The entire plate 16 is transparent, but for operation of the sampling unit 2 (as further described below) it is only necessary that the bottoms of the wells 18 are transparent so as to enable light to be passed

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therethrough. The wells 18 of the plate 16 are each adapted to hold a sample of blood. With a plate 16 placed on the support tray 4 in the loading position, the tray 4 may be moved by the servo drive mechanism so as to place the tray 4 and plate 16 in a retracted (scanning) position 20 within the sampling unit 2. The sampling unit 2 includes a keypad 22 disposed on the front panel 24 of the sampling unit 2 and associated with the control circuitry. The keypad 22 is used as the user interface to select the functions of the sampling unit 2, including movement of the support tray 4, which are controlled by the control circuitry. A liquid crystal display (LCD) panel 203 is also provided, in association with the keypad 22, to provide feedback and prompts to an operator with respect to the functions of the sampling unit 2 and the control circuitry.

Referring to Figures 12, 13 and 14, the optical analysis of samples held in the wells 18 of a sample plate 16 can be critically dependent on the position of the wells 18 of a sample plate 16 with respect to the video camera 10. Sample plates 16 often vary slightly, for instance between manufacturers, as to outer dimensions, this potentially leading to discrepancies of several pixels between ostensibly corresponding wells 18 on different plates 16. However, the plates 16 of a single manufacturer will generally be identical and it is therefore possible to preset the apparatus in terms of well position, with respect to a calibrating plate of a batch of plates 16 such that subsequent plates 16 of the batch can be read under effectively identical conditions without resetting of the

apparatus. Such presetting can be done by image analysis of the calibrating plate so as to establish the centre point of a corner well 18 with respect to the camera 10. Presetting in this way however depends on very accurate reproducibility of the position of each plate 16 in a batch when loaded, with respect to the camera 10.

The variations which occur with respect to sample plate 16 include a tolerance of 0.5 mm in length, and variation in cross sectional shape of the edge configuration of the plates. The pitch and number of wells 18 on each plate 16 are standard but can vary in position along the length of the plate.

The sample plate 16 is loaded in a sliding carriage 302 which comprises a precision machined or molded body which slides horizontally into the retracted position 20 above the panel 42 of electroluminescent material. Linear bearings are fitted to the sliding carriage 302 to effect both smooth and precise location of the carriage at its stop positions and also during the extent of its travel. The sliding carriage 302 forms part of the support tray 4, referred to above.

The sample plate 16 is received in a shallow recess in the sliding carriage 302. Three indexing stops 308, 309 and 310 are provided at the edges of the shallow recess 325 for accurate location of the plate 16 when loaded. The recess 325 is large enough with respect to the plate 16 to give peripheral play between the edges of the plate 16 and the recess 325, this allowing access for the plate 16 and to

accommodate slight variation in plate sizes. A locking mechanism 326 is provided to lock the plate 16 into position against the indexing stops 308, 309 and 310, which mechanism operates automatically on loading of the support tray 4 into the retracted position 20. The locking mechanism 326 is located on the sliding carriage 302, adjacent the plate recess 325. Beneath the plate 16 when loaded in the sliding carriage 302 is an aperture large enough to enable illumination of the plate 16 by the electro-illuminescent panel 42.

The locking mechanism 326 comprises a pair of pivoting levers 311 and 312, mounted on pivot pins 320 and 319 respectively. Each lever 311, 312 is provided with a finger 306, 307, which fingers operate on the plate 16 to push it against the indexing stops 308, 309 and 310. Both levers 311 and 312 are operated by means of a heel 305 which is engaged by a cam actuator 304 as the sliding carriage 302 moves into the retracted position 20. The two levers 311 and 312 and the heel 305 are connected in series, firstly by a pull rod 323 between the two levers 311 and 312, and secondly by the lever arm 318. The pull rod 323 is shaped so as to have an elbow 316 such that the two levers 311 and 312 at rest are arranged generally perpendicular to one another, their respective fingers 306 and 307 being directed towards two adjacent sides of the plate 16. The first lever 312 connected in series with the heel 305 is arranged with respect to its pivot pin 319 such that when the heel 305 is displaced by the cam actuator 304, the lever 312 rotates in a clockwise direction. The pull rod 323, however, is arranged

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with respect to the pivot pin 320 on the other lever 311, and by means of the elbow 316 such that movement of the heel 305 operates to turn the second lever 311 in an anti clockwise direction. When the cam actuator 304 acts on the heel 305 to move it in a downwards direction according to arrow E in Figure 13b, the lever arm 318 rotates the attached lever 312 in a clock wise direction, this having the effect of moving the elbow 316 of the pull rod 323 also in the direction of the arrow E. Because the pull rod 323 is significantly further spaced from the pivot pin 320 on the second lever 311, the effect of the movement of the elbow 316 on this second lever 311 is significantly greater that the effect of the lever arm 318 on the first lever 312. Therefore, when the heel 305 is moved downwards, it is the second lever 311 which comes into contact with the plate 16, this having the effect that the plate is first pushed side ways against the side indexing stop 308 as the sliding carriage 302 moves into the retracted position 20.

Referring to Figure 13c, as the sliding carriage 302 continues to move, and the heel 305 is therefore moved further in the direction of the arrow E, the second lever 311 is prevented from further rotation in the direction of the arrow G because the finger 306 is already in contact with the plate 16. Because pull rod 323 is more flexible than lever arm 318, the effect at this stage is that the first lever 312 continues to rotate in the direction F, brings the finger 307 into contact with the lower edge of the plate 16, the pull rod 323 being deformed thereby. Also because the pull rod 323 is relatively

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flexible, the force applied by the finger 306 against the side of the plate 16 is relatively low, such that the pressure of the finger 307 of the first lever 312 is able slide the plate 16 against the upper edge indexing stops 309 and 310, past the finger 306. Hence the plate 16 is very accurately positioned against the indexing stops 308, 309 and 310 by a two part lever action, actuated simply by the movement of the sliding carriage 302 into its retracted position 20. (The first lever 312 is centrally located with respect to the tray 16 such that places it symmetrically with respect to the upper stops 309, 310.)

The elbow 316 travels an arc which is approximately two thirds of the travel of the finger 307. However, because the pull rod 323 joins the second lever 311 at a significant distance from the relevant pivot pin 320, the lever 311 is very sensitive to movement of the elbow 316 and rotates substantially further, in the anti clockwise direction, than does the first lever 312 under the same displacement of the heel 305.

The lever arm 318 is sufficiently flexible that minor overriding of the cam actuator 304 with respect to the heel 305 can be accommodated. This limits the overall locking forces which can be applied to the plate 16 by the fingers 306 and 307. When the sliding carriage 302 is brought out of the retracted position, into a loading position, the locking mechanism 326 relaxes to a position where the plate 16 is free to be removed, these fingers 306 and 307 spring away from the side and lower edge of the

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plate 16.

The locking mechanism 326 employs a particularly advantageous combination of principles and provides a single piece combination crank and lever arrangement which operates simultaneously in opposite directions. Sequential action of the fingers 306, 307 creates an order in the positioning of the plate 16 with respect to the stops 308, 309 and 310, this being first to the side and then upwards against the upper stops 309, 310. The mechanism 326 is utilised only while a plate 16 is installed in the apparatus for reading, and is not normally flexed. Thus, the mechanism is less subject to ageing deterioration. Further, being a 1-piece component, it is particularly easy to manufacture, assembly and maintain.

Referring to Figure 14, a manual override is provided such that the locking mechanism 326 can be tested, or can be set in cases where there is doubt that the automatic setting is operating according to design. The manual override is operated by means of a pin 327 which cooperates with an L-shaped aperture 328 in the sliding carriage 302. The pin 327 is mounted on a further, short lever 329 which in turn is connected to the heel 305. During automatic operation of the locking mechanism 326, the pin 327 is seated at the upper end of the long portion of the L-shaped aperture 328, and is free to travel up and down the aperture 328 during operation of the mechanism 326. However, in manual override, the pin 327 is brought down into the short arm of the aperture 328, (as shown in Figure 14) this having the

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same effect on the heel 305 as would the cam actuator 304. The shorter arm of the aperture 328 is slightly enlarged upwards such that the pin 327 seats in the shorter arm under the

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resilient, returning forces exerted by the two levers 311 and 312. This further lever 329 is necessarily slightly resilient in order to accommodate a sideways movement of the pin 327 into the shorter arm of the aperture 328.

Referring to Figures 4 and 5, a series of optically activated switches are disposed in the unit 2 so as to activate lighting circuitry 40 of the unit 2 when the plate 16 is correctly placed in the retracted position 20 above a panel 42 of electroluminescent material. The lighting circuitry 40 supplies power to the panel 42 so as to cause the panel 42 to illuminate the plate 16 with an even light. The light from the panel 42 passes through the plate 16, and in particular any blood samples disposed in the wells 18, and is received by the camera 10 after being collected by a correcting lens 204 (further described below) and reflected from a mirror plate 44.

The arrangement of the camera 10 with respect to the sample plate 6 is particularly compact. Firstly, the mirror plate 44 "folds" the light transmitted through the plate 16 to the camera 10 so that the camera 10 can be positioned horizontally in the unit 2. This allows the unit 2 to be designed without the height that would be necessary to accommodate a vertical camera 10. Secondly, the camera 10 has a relatively short focal length, of the order of 270 mm.

The focal plane of the horizontally positioned camera 10 is perpendicular to the plane of

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the plate 16, the mirror plate 44 being disposed at an angle of 45° with respect to the plate 16. The mirror plate 44 is a front surfaced, precision ground mirror which is mounted so as to be operator-adjustable along perpendicular axes, this allowing alignment to be carried out in setting up the apparatus. It comprises plate glass, having an aluminium coat and quartz overcoat, and is polished to an optical flatness of within two fringes. The centre of the mirror plate 44 lies 155 mm from the camera 10 and 132 mm from the sample plate 16. It is removable from the unit 2 for cleaning and maintenance purposes.

Between the mirror plate 44 and the support tray 4 is provided the correcting lens 204 which adjusts the image viewed by the camera 10 with respect to the edges of a sample plate 16. The wells 18 are each of the order of 1 cm deep and without the lens 204 as shown in the inset 212 of Figure 6, portions 210 of samples 211 contained in wells 8 towards said edges tend to be partially obscured by the walls of the wells 18 themselves which overshadow the samples in the diverging field of view 213 of the camera. The lens 204 adjusts that field of view so that the camera 10 effectively looks directly down into all wells 18 by virtue of creating a non-converging section 205 of the field of view.

The lens 204 comprises a 4" by 5" rectangular 100 mm x 125mm biconvex, 2 x power lens made by Bausch and Lomb, under reference number 81-33-90. It can comprise a plastics material where a test being carried out on samples is not affected

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by the spectral transmission properties of the lens 204, but in some circumstances it will be necessary to use a lens 204 of particular transmission characteristics. For instance, it may be necessary to use a lens, in spite of the high relative of compared with plastics materials.

The illuminating panel 42 comprises a white light source in the form of an electroluminescent plate sandwiched between diffusing layers. This type of source has the advantages of being physically of very low profile while generating very evenly distributed white light without generating significant heat. This latter is clearly an important feature for instance with medical samples which may be badly affected by hot light sources. As mentioned above, some optical sample analysis tests are colour dependent and it can therefore also be important that the light source is spectrally flat, as well as being spatially evenly distributed so as not to bias the results with respect to selected samples. Various electroluminescent lights are known, and the principles behind them are discussed in the following publications: "Australian Firm Develops New EL Technology" by Jim Rowe, published in ELECTRONICS AUSTRALIA, in August, 1988, and "Cold Light, Hot Prospects" by Athol Yates, published in DESIGN WORLD

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No 16, in 1989. Particularly suitable is the flexible electroluminescent light known as "E'LITE", marketed by the company UNIVERSAL FIBRE OPTICAL CORP. P/L and also described in the two publications referred to.

The apparatus as a whole is powered by direct current and the lighting circuitry 40 provides even light by generating an alternating current (necessary to activate the panel 42) from the 12 volt direct current source by "chopping" the direct current at a relatively high frequency with respect to the operation of the camera 10. It is important that light levels remain even to avoid temporal fluctuations which may affect sample analysis. By using a "chopped" direct current, fluctuations in an external alternating power source are avoided but it has been found important that the frequency of the generated alternating current should be high enough that the camera 10 effectively integrates several cycles in producing each pixel of a scanned image of a sample plate 16. Using a conventional video camera, a frequency of 100Hz has been found suitable, the wave form being substantially a sine wave. The use of a chopped direct current power source is also advantageous in that a dual voltage supply can be provided for use in countries with different network supply voltages, and it is relatively electrically safe compared with equipment running direct from a mains supply.

Referring to Figures 5 and 15, the image of the plate 16 displayed on the monitor 6 may be a substantially real-time image obtained from the

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camera 10, or it may be a stored image. The apparatus is provided with two memory areas for image data obtained from the camera 10. One of these, the "grab" memory, is continually updated by digitised in-coming image data. This provides the substantially real-time image. The other, the "snap" memory, stores a digitised frozen image, only updated or

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replaced under a positive control step taken by means of the personal computer 9. An image displayed from the "snap" memory may be manipulated under the control of the personal computer 9 for instance so as to overlay stored or reference images. Hence, the image provided by the monitor 6 can be used to observe samples currently in situ, or to consider images previously obtained. In general, the monitor 6 is used to display the "grab" image so that easy visual checks can be made in use of the apparatus for instance a sample plate 16 is present, while the "snap" image is displayed on the computer screen 30 where detailed analysis and comparisons can be carried out. (The "grab" image is real time except for two conversion steps between digital and analogue formats.) The image displayed on the monitor 6 is displayed under the microprocessor control by the control circuitry, the personal computer 9 being involved only in manipulating the "snap" image.

To set up the apparatus for use, a laser replaces the camera 10 and the mirror plate 44 and correcting lens 204 are adjusted such that the laser beam is reflected by the mirror plate 44 and transmitted by the lens 204 onto a predetermined reference point on the support tray 4.

To conduct an analysis of blood samples disposed in the plate 16, the sampling unit 2, in particular the personal computer 9, is connected to the colour monitor 30, a keyboard 32 and preferably a printer 34 so as to form an apparatus 36 for analysing the samples, as illustrated in Figure 5. The monitor 30 and keyboard 32 are required to enable

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a user to instruct the sampling unit 2 as to the evaluation to be performed on the samples in the plate 16, inter alia. The number of tasks which the sampling unit 2 can be instructed to perform is determined primarily by the software stored in the personal computer 9, and this enables the sampling unit 2 to operate as described hereinafter with reference to the flow diagram illustrated in Figures 9, 10 and 11. The images to be received are then calibrated by means of a blanking step with respect to an empty reference sample tray to eradicate distortions introduced by the sample trays themselves.

On activating the sampling unit 2 and thereby initialising the personal computer 9, the unit 2 begins operating at step 100 of the flow diagram, at which the unit 2 places an introductory display on the colour monitor 30. A user is then able to move through the steps of the flow diagram by inputting correct commands to the unit 2 using the keyboard 32. From the introductory display step 100 a user is able to proceed to step 102 at which a main menu display is generated on the colour monitor 30. The main menu lists a number of options from which the user may make a selection, including entry into a number of subroutines, such as "photo-plate", "save photo-plate image", "display photo-plate", and "plate function analysis". If an option is not selected within a predetermined period of time on entering step 102, operation of the unit 2 returns to the introductory display step 100 via step 104, which is entered into on expiration of the predetermined period, as monitored by a timing circuit in the unit 2.

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On entering the photo-plate subroutine which begins at step 106 a user is able to view the "grab"

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image presented on the monitor 6 and select an instant at which he wishes to record the image. Proceeding to "grab mode" at step 108 causes an image processing circuit of the computer 9 to access the signal outputted to the monitor 6, this comprising an array of pixels which is representative of the image displayed at the instant step 108 is entered into. The image processing circuit selects one field of the output of the camera 10 and converts the analog signal representative of the field into digital picture information having a 512 x 512 pixel resolution. Each pixel is stored as an 8 bit value in a memory of the computer 9. Therefore each pixel represents one of 256 shades of grey and the 8 bit value is hereinafter referred to as a grey-level value. The stored pixels include pixels which specifically relate to the intensity of light having passed through the wells 18 of the plate 16 and provide sufficient information to determine a number of characteristics of the blood samples disposed in the wells 18. There are approximately 700 pixels stored for each well 18 and the image of the plate 16, which can include up to 96 samples, is read and recorded in 1/25 of a second. On completing step 108 the unit 2 returns operation to the main menu step 102.

An image retrieved at step 108 can be stored on a disc in the disc drive 8 on entering the save photo-plate image subroutine at step 110. A list of the files currently stored on the disc is provided on the colour monitor 30 at step 112 and then by entering a file name at step 114 the retrieved image is stored on the disc under the chosen file name.

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The unit 2 then reverts to the main menu stop 102. An image may be retrieved from disc in a similar fashion to the storage procedure by entering the restore photo-plate subroutine at step 116 which on completion returns to the main menu step 102. The ability to store and retrieve images on discs enables a user to retain basic information with respect to samples for later use, which is particularly advantageous if further analysis is required at a later stage.

By entering the display photo-plate subroutine at step 118 the image stored in memory of the computer circuitry 9 can be displayed on the colour monitor 30 in a number of formats. At step 120 the format options which are available are displayed and if display of the entire image is selected the unit 2 proceeds to step 122 whereas if display of a particular area of the plate represented by the image is desired then operation should be continued at step 124 which is the beginning of a display selected plate subroutine. After step 124 a menu is displayed at step 126 which provides a list of area selection options such as whether display of a selected well is required. Two of the options are illustrated in Figure 5 being display of the selected well at step 128 and display of the optical density of a selected pixel at step 130. The optical density is a value which is obtained from the grey level-value of a selected pixel. Display of any part of the image on the colour monitor 30 is effected by allocating a colour to each of the relevant pixels required to make up the display on the basis of the grey-level value of each pixel. The display selected

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plate subroutine 124 and the display entire image step 122 both return operation of the unit 2 to step 120 on completion.

The plate function analysis subroutine begins at step 132, as shown in Figure 6, and proceeds to step 134 at which a menu is displayed which enables a user to select what type of analysis is to be performed on the blood samples of a plate 16, which has an image thereof stored in the computer circuitry. The options which are available include detecting the presence of a virus, detecting the presence of agglutination in samples to determine blood group or type and conducting spectrophotometer or coagulation analysis of the samples. Each of these analysis operations are performed by entering into one of the "ELISA (enzyme linked immuno sorbent assay) reader mode" subroutine at step 136, the "agglutination reader mode" subroutine at step 138, the "spectrophotometer mode" subroutine at step 140, or the "coagulation mode" subroutine at step 190, respectively.

On selecting the ELISA reader mode subroutine operation of the sampling unit 2 proceeds to step 142 at which an ELISA mode menu is displayed and gives the user an option of examining the pixel data of a stored image manually by entering a "raw data subroutine" at step 144 or analysing the relevant pixel data of the stored image using an established protocol by entering a "stored protocols subroutine" at step 146. At step 144 of the raw data subroutine a raw data menu is displayed listing the data processing options which are available such as

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creating a new plate image by excluding the data relating to samples which are of no interest at step 148, loading a plate image from disc into memory of the computer circuitry 9 at step 150 and reading the plate image stored in the memory at step 152. On reading a selected image at step 152 the central 3 x 3 array of pixels which each relate to the centre of a respective blood sample are accessed and their grey-level values processed so as to obtain an average grey-level value for each blood sample of the image read. The average grey-level values are converted to optical density values which are then either displayed on the colour monitor 30 at step 154 or outputted on the printer 34 at step 156. The optical density values may be displayed numerically at step 154 or pictorially by allocating colour on the basis of the size of the optical density values or whether they fall within a particular range. The average grey-level values may also be similarly used instead of the optical density values as a basis for generating the pictorial display. On exiting the raw data subroutine operation of the sampling unit 2 returns to the plate function analysis menu step 134.

The stored protocols subroutine begins at step 146 at which a number of available protocols for analysing blood samples using optical density values are displayed. The protocols include established methods of determining the existence of the AIDS and hepatitis viruses in a sample using optical density values. Each of the protocols performs an analysis by first calculating one or more reference values and then comparing the data of the samples to be tested with the reference values. A medium cut-off

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reference value is always determined and all of the samples having an optical density value higher than the cut-off value are considered to be positive and therefore contain the virus for which the analysis is being performed. Similarly if the optical density value of a sample is lower than the cut-off value then it is considered to be negative. A number of the available protocols also determine one or more positive or negative reference values in addition to a medium cut-off value and these can be used to determine the extent to which a sample is positive or negative. These positive or negative reference values are also referred to as cut-off values. The cut-off values are all derived using pixel data corresponding to a predetermined number of positive and negative reference control samples which are included in the plates 16 amongst the samples to be tested. The content of the control samples is chosen in accordance with the analysis to be performed and the control samples are placed in a predetermined position in the plate 16, such as at one end of an end column of the plate 16, whilst in the ELISA reader mode subroutine the optical density value of each blood sample is derived from the mean value of the 9 grey-level values of the 3 x 3 array of pixels which are representative of the centre of a sample.

On selecting a protocol to be used at step 146 operation of the sampling unit 2 proceeds to step 158 at which a number of options are displayed in a protocol menu to facilitate implementation of the selected protocol. Requesting display of a plate map causes operation to proceed to step 160, at which a map of the plate 16 is displayed indicating which

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wells 18 the selected protocol proposes to regard as containing positive and negative control samples, and which wells 18 the selected protocol proposes to regard as comprising test samples. Operation is returned to step 158 on completing step 160. An adjustment of the wells 18 which are to be regarded as containing positive control samples can be made by entering a positive control menu at step 162 from step 158. Similarly an adjustment with respect to which wells 18 are to be regarded as containing negative control samples can be made by entering a negative control menu at step 164 from step 158. The extent of the adjustment which can be made at steps 162 and 164 will, of course, depend on the protocol selected at step 146, i.e. only a certain number of positive and negative control samples may be recognised and perhaps only those in a particular position can be recognised. An adjustment can also be made with respect to the number of samples which are to be analysed by entering a number of unknown samples menu at step 166 from step 158.

Once a user is satisfied with respect to the samples to be analysed and the samples which are to be used by the selected protocol as control samples, the array of pixels representative of a plate image, stored in the computer circuitry 9, is read at step 168 and optical density values for each of the relevant samples are determined. The cut-off values for the selected protocol are then calculated at step 170 and can be displayed numerically at step 172 or graphically on an x/y plot at step 174. Operation of the sampling unit 2 is then returned to the selected protocol menu step 158.

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After deriving the cut-off values and the optical density values for each of the relevant samples the results of the analysis can be outputted by entering an "output results" subroutine at step 176, as shown in Figure 7. The results, i.e. whether the test samples are positive or negative, are available on completing the calculate cut-off values step 170 and can be displayed and retrieved in a number of ways. At step 176 an output results menu is displayed which lists a number of options which are available to the user for display and retrieval of the results. By proceeding at step 178, the results may be displayed on the colour monitor 30 as a number of optical density values together with an indication as to whether a value represents a high positive, a low positive, a high negative or a low negative, and can then be scrolled through at step 180. The results may also be displayed graphically on the colour monitor 30 in a number of formats. Proceeding to step 182 the results are outputted on the printer 34 and proceeding to step 184 the results are recorded on a disc in the disc drive 8 after entering a file name at step 186. On completing the output results subroutine operation of the sampling unit 2 is returned to the select stored protocol menu step 158 from which operation can be returned to the main menu step 102.

The spectrophotometer mode subroutine may operate in a similar manner to the ELISA reader mode subroutine and a detailed illustration of its operation is not provided in Figures 6 and 7. The "agglutination" reader mode subroutine involves a

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test with respect to blood grouping and type and either 8 or 12 distinct blood specimens are tested for each plate 16, depending on the precision of the evaluation required. If 8 distinct specimens are tested 12 samples of each specimen are placed in a row of wells 18 of the plate 16 and 12 different reagents are used on each specimen, whereas if 12 distinct specimens are to be tested a sample of each specimen is placed in a column of wells 18 of the plate 16 and 8 different reagents are added. In one type of agglutination test the samples are each examined to determine whether they have reacted to the reagent deposited therein by agglutinating, which indicates that the corresponding specimen belongs to the blood group or type which the reactive reagent is specifically adapted to test for. To place any agglutinated blood in the centre of the wells 18 the plate 16 is normally centrifuged before being placed within the sampling unit 2. The unit 2 then accesses a pixel for each sample that corresponds substantially to the centre of the respective well 18. The value of each pixel is then compared with a reference value to determine whether the pixel represents the presence of agglutinated blood. The display capabilities of the unit 2, as described previously, may also be used to search for agglutinated blood in a sample.

Using the spectrophotometer mode subroutine a variety of tests can be performed. The subroutine generally involves obtaining optical density values for each of the wells 18 or relevant samples and analysing the values to determine the presence of particular colours or any changes in colour.

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As is apparent from the previous description, the sampling unit 2 significantly simplifies the analysis of blood samples by automating as much of the process as possible, reduces the time taken to obtain appropriate data on a plurality of samples and provides a user with a significant degree of flexibility. The unit 2 also removes the human error element with respect to handling the data.

Many modifications will be apparent to those skilled in the art without departing from the scope of the present invention as hereinbefore described with reference to the accompanying drawings.

For instance, although described with reference to blood sample analysis, other fluids such as biological or industrial fluid samples may be tested by use of apparatus according to an embodiment of the invention.

Although as described control circuitry for controlling mechanical operations of the sampling unit 2 is housed in a section of the unit 2, it may instead be incorporated in the operations of the personal computer 9. This also may mean that the LCD panel 203 and the keypad 22 are redundant. Another optional function of the control circuitry, whether separate from or incorporated in the personal computer 9, may be to provide clock and calendar information with respect to sample analysis. This can be particularly relevant where samples are of a type which is unstable. For instance, in some blood

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analysis tests there is only a relatively narrow window of about a quarter of an hour within which each sample can be read, this window occurring some two hours after the sample has been initiated.

A hard copy printer may be provided for producing hard copies of images output by the computer 9. These can be used for instance for visual analysis or records purposes, or to "fix" a changing sample state for analysis at a later time and over a longer period than might otherwise by available.

Although the apparatus is described with reference to images having 512 x 512 pixel resolution, it will be clear that the resolution may be significantly changed without departing from the present invention.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Apparatus for use in analysing fluid samples comprising:

means for illuminating a device, which includes a plurality of receptacles arranged in an array, at least one receptacle of the array having a sample disposed therein, so as to pass light through or reflect light from said receptacles;

camera means responsive to said light passed through or reflected from said receptacles for generating a video signal representative of the intensity of light passed through or reflected from the receptacles; and

processing means for processing said video signal, deriving from said video signal an array of pixels representative of said intensity at a predetermined instant, storing said array of pixels and processing stored pixels to determine if said sample has a predetermined characteristic.

2. Apparatus according to claim 1 which further comprises receiving means for receiving said device.

3. Apparatus according to claim 1 wherein said receiving means comprises a support for said device, said support being provided with at least three location means for locating consecutive devices of a series of devices in a reproducible position on said support.

4. Apparatus according to either one of claims 2 or 3 which further comprises a housing which

accommodates said camera means and said receiving means.

5. Apparatus according to claim 4 wherein said camera has a viewing aperture which is significantly smaller in at least one dimension than the area of the device over which said array of receptacles is disposed, there being provided image correction means between the camera and the device.

6. Apparatus according to claim 5 wherein said image correction means comprises a lens which is optically passive in its central area but which is image modifying adjacent its periphery.

7. Apparatus according to either one of claims 5 or 6 wherein said image correction means comprises a material which is optically transparent over a broad spectral range.

8. Apparatus according to claim 7 wherein said material comprises glass.

9. Apparatus according to any preceding claim wherein said array is substantially planar and said camera means is arranged such that it has a viewing aperture which is disposed in a plane which is not parallel with respect to the array when an associated device is installed in the apparatus for sample analysis.

10. Apparatus according to claim 9 wherein reflecting means is arranged between the position of an array of a device when installed in the apparatus

for sample analysis, and said viewing aperture, to reflect light passed through or reflected from said receptacles to said viewing aperture.

11. Apparatus according to either one of claims 9 or 10 wherein the plane of the viewing aperture is substantially perpendicular, or perpendicular, to the array of a device when installed in the apparatus for sample analysis.

12. Apparatus according to claim 4 wherein said receiving means comprises a support for said device, which support can be moved between a loading position in which it lies external to the housing for loading or unloading a device, and a scanning position in which it lies inside the housing for scanning of samples disposed in receptacles of the device by said camera means.

13. Apparatus according to any preceding claim wherein a plurality of receptacles have samples disposed therein, and wherein said samples include at least one reference sample and said processing means uses at least one pixel corresponding to said at least one reference sample to derive a reference value and the existence of said predetermined characteristic for each sample is determined by comparing said reference value with a value derived for the sample from at least one pixel corresponding thereto.

14. Apparatus according to claim 13 wherein said processing means is adapted to use said value for the samples to drive a colour display means, wherein a

colour displayed to represent a sample is selected on the basis of whether the corresponding value lies in a range which corresponds to said colour.

15. Apparatus according to any one of claims 1 to 13 wherein said processing means is adapted to use said stored array of pixels to drive a colour display means.

16. Apparatus according to any one of claims 2 to 15 which comprises a sampling unit which includes said receiving means, said illuminating means, said camera means, said processing means, and a display means which can be driven in real time by said video signal, or substantially in real time by said stored array of pixels.

17. A positioning mechanism for use in positioning an article in a reference position with respect to first and second axes, comprising first and second pivotally mounted levers, each lever having a bearing portion for bearing on the article and applying a force along a respective one of said first and second axes, and coupling means for coupling the levers such that pivotting of either lever in a first rotational direction acts to pivot the other lever in the other rotational direction, wherein said bearing portions are each offset with respect to the pivot point of its respective lever in a direction substantially perpendicular to respective ones of said first and second axes, such that said pivotting of either lever acts so as to move each said bearing portion in a direction at least substantially along its respective axis.

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18. A positioning mechanism according to claim 17 wherein said levers have different mechanical advantages.

19. A positioning mechanism according to either one of claims 17 or 18 wherein said first and second axes are perpendicular.

20. A positioning mechanism according to any one of claims 17, 18 or 19 wherein said coupling means comprises a substantially L-shaped arm.

21. A positioning mechanism according to any one of claims 17 to 20 wherein operating means is provided to pivot the first lever so as to apply its bearing portion against the article, the bearing portion of the second lever coming into contact with the article before the bearing portion of the first lever comes into contact with the article on operation of said operating means, such that the article is positioned along each axis consecutively on operation of the operating means.

22. A positioning mechanism according to claim 21 wherein said coupling means is more resilient than said operating means so as to accommodate further pivotting of the first lever after the bearing portion of said second lever is already in contact with the article.

23. A positioning mechanism according to any one of claims 17 to 22 wherein said levers and coupling means comprise a single shaped component of resilient

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material.

24. Viewing apparatus for use in optical sample evaluation of planar sample arrays, comprising a video camera having a relatively short focal length, arranged such that the central axis of the field of view of the camera is substantially perpendicular to the plane of a sample array during evaluation, there being provided reflecting means such that the camera provides an image of said array, there being further provided a correcting lens for correcting marginal distortion of said image.

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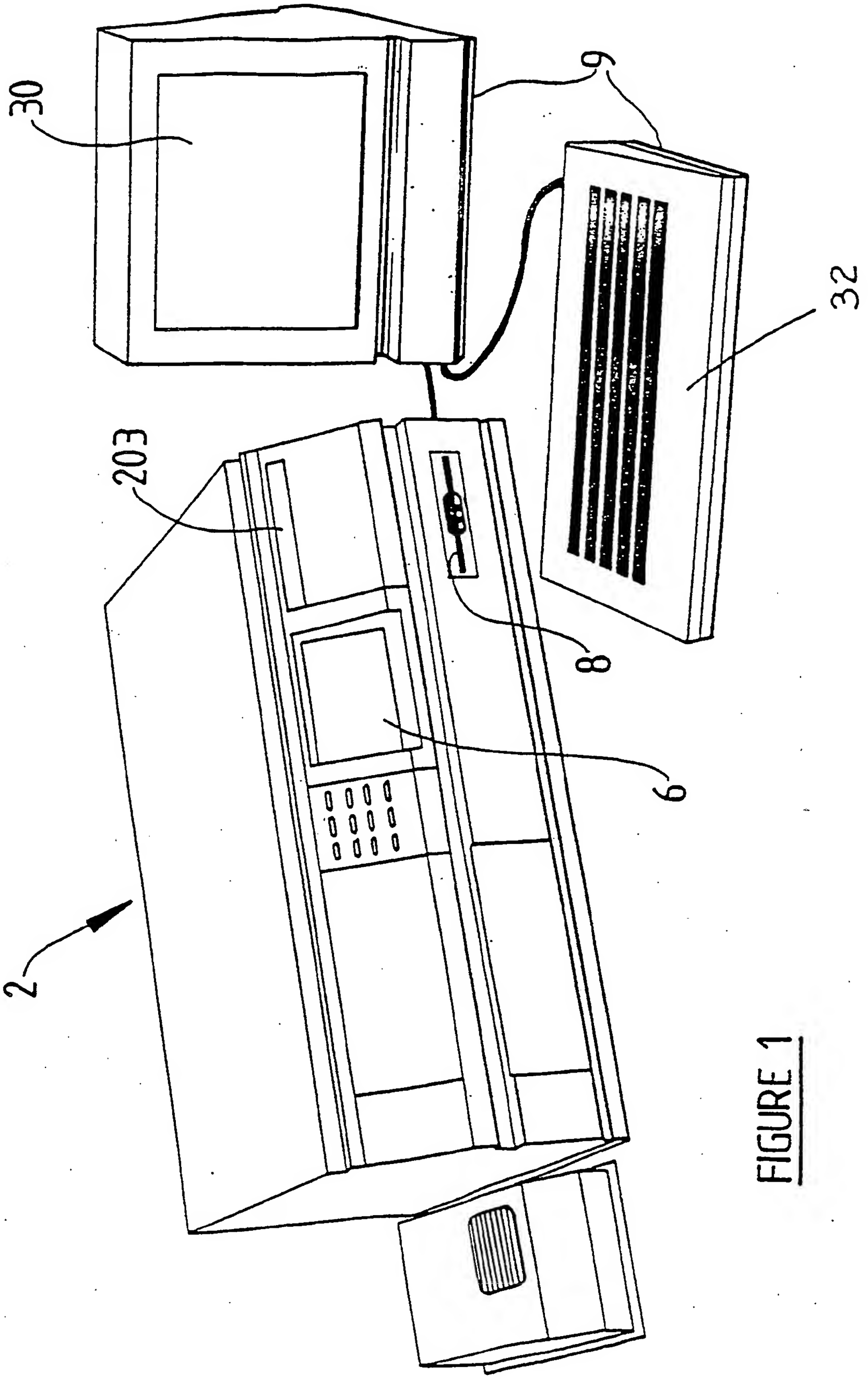

FIGURE 1

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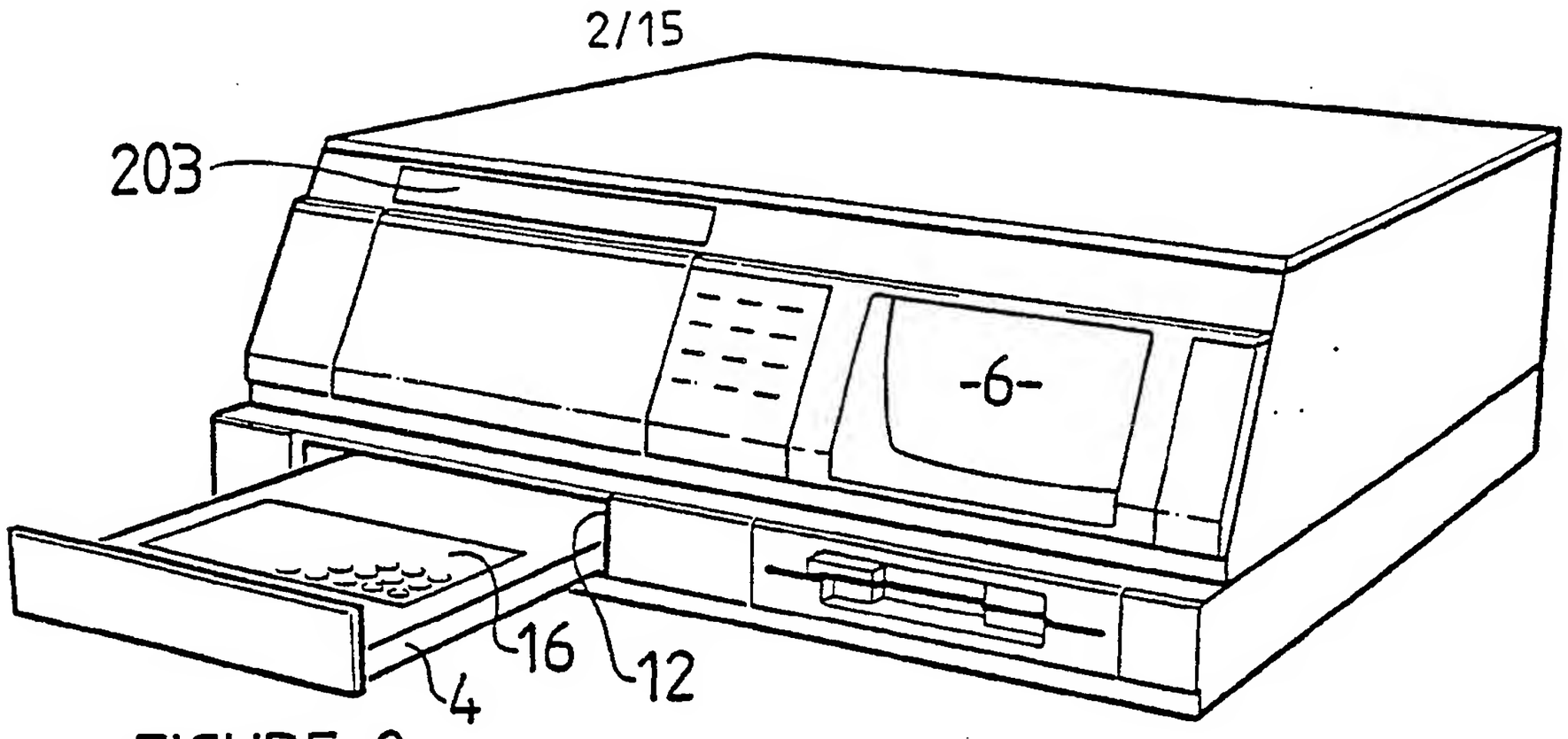


FIGURE 2

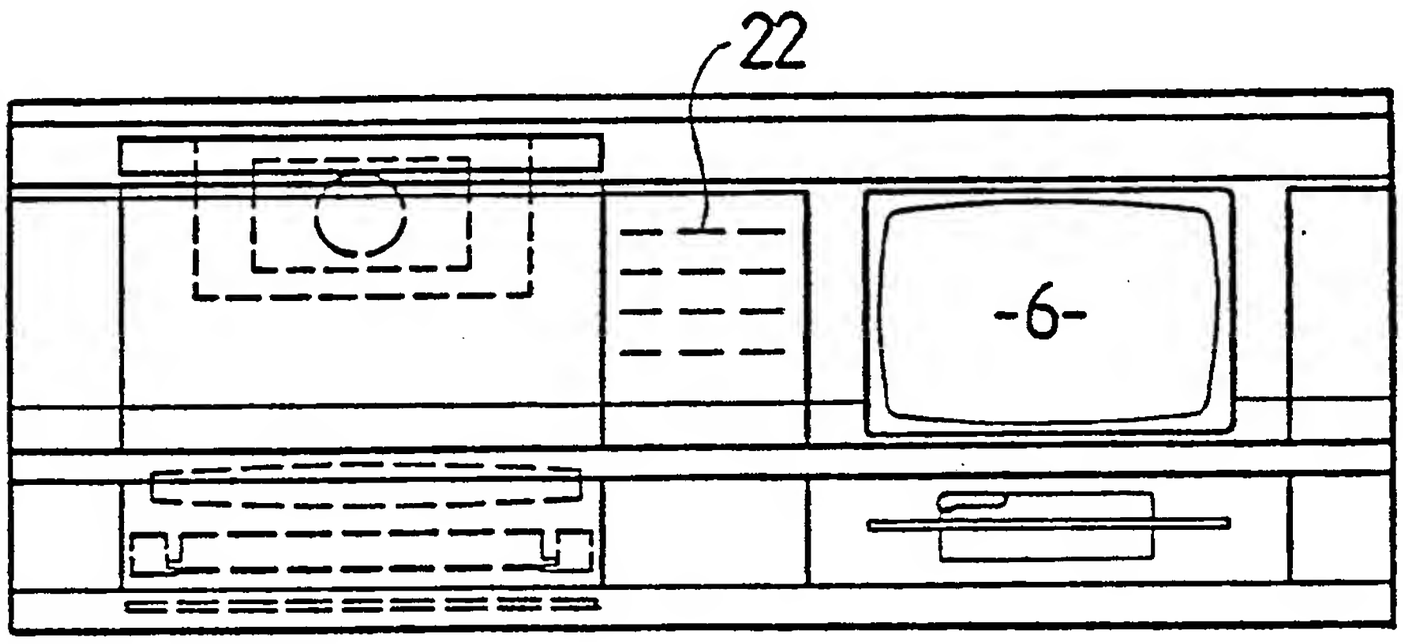
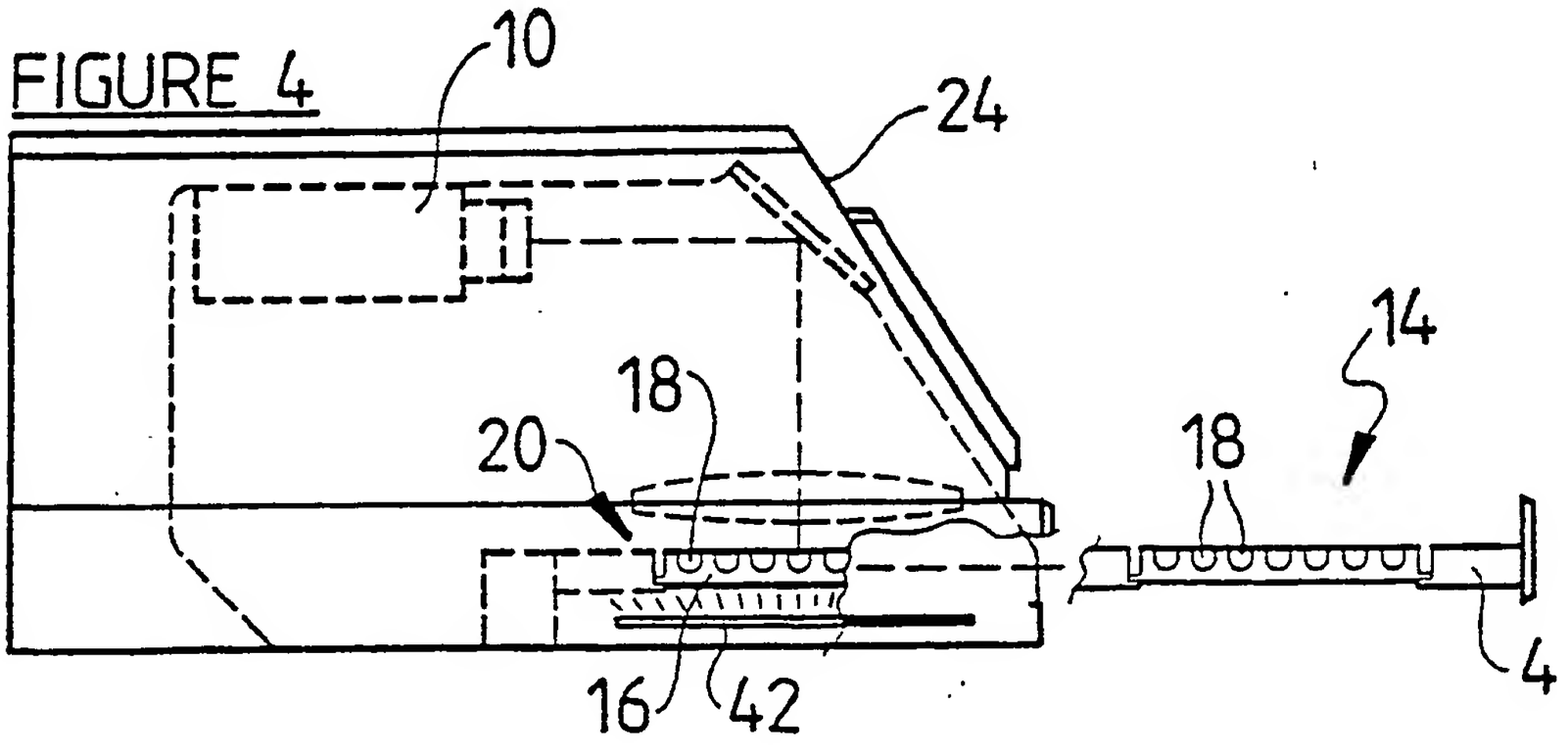


FIGURE 3

FIGURE 4



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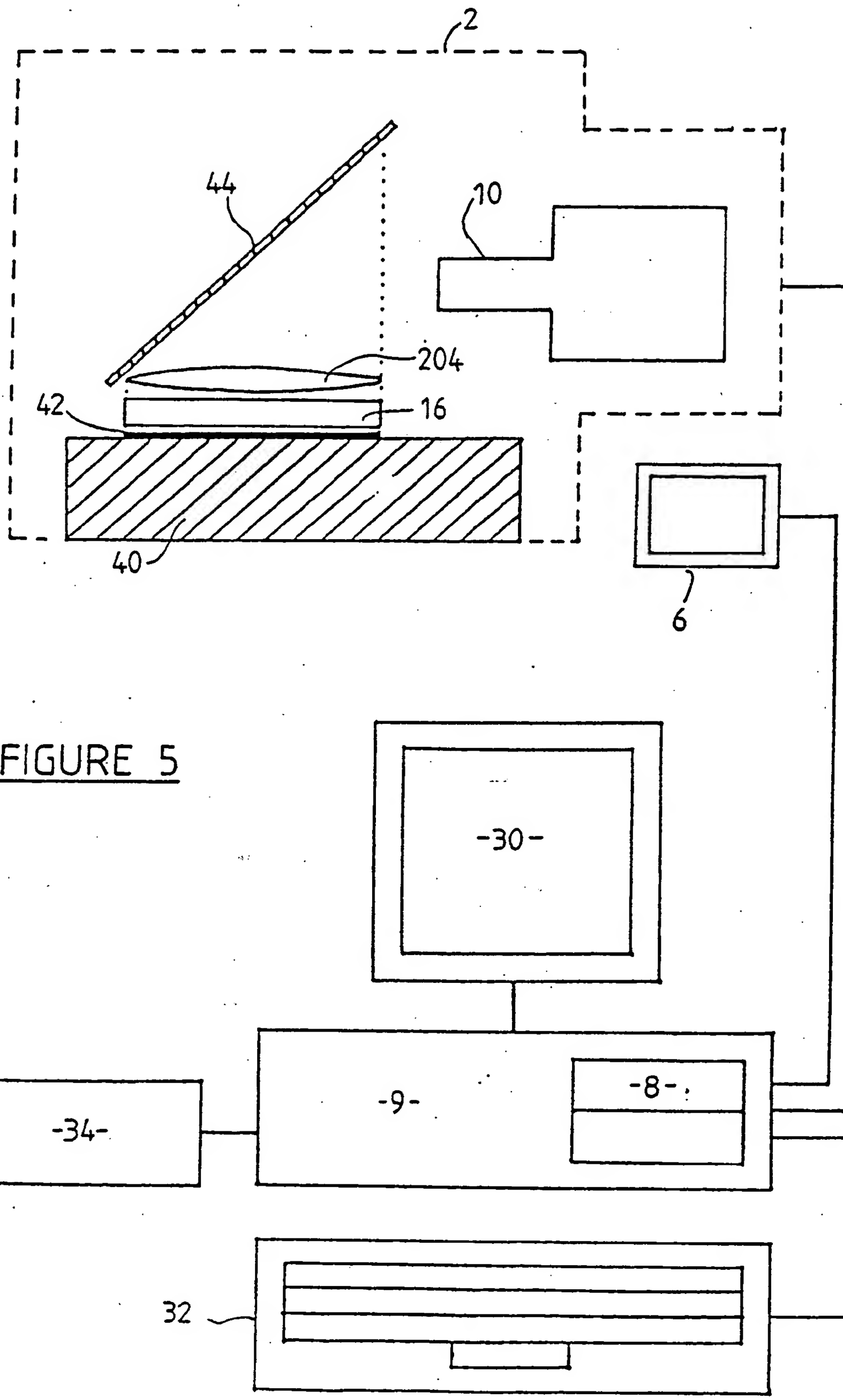

FIGURE 5

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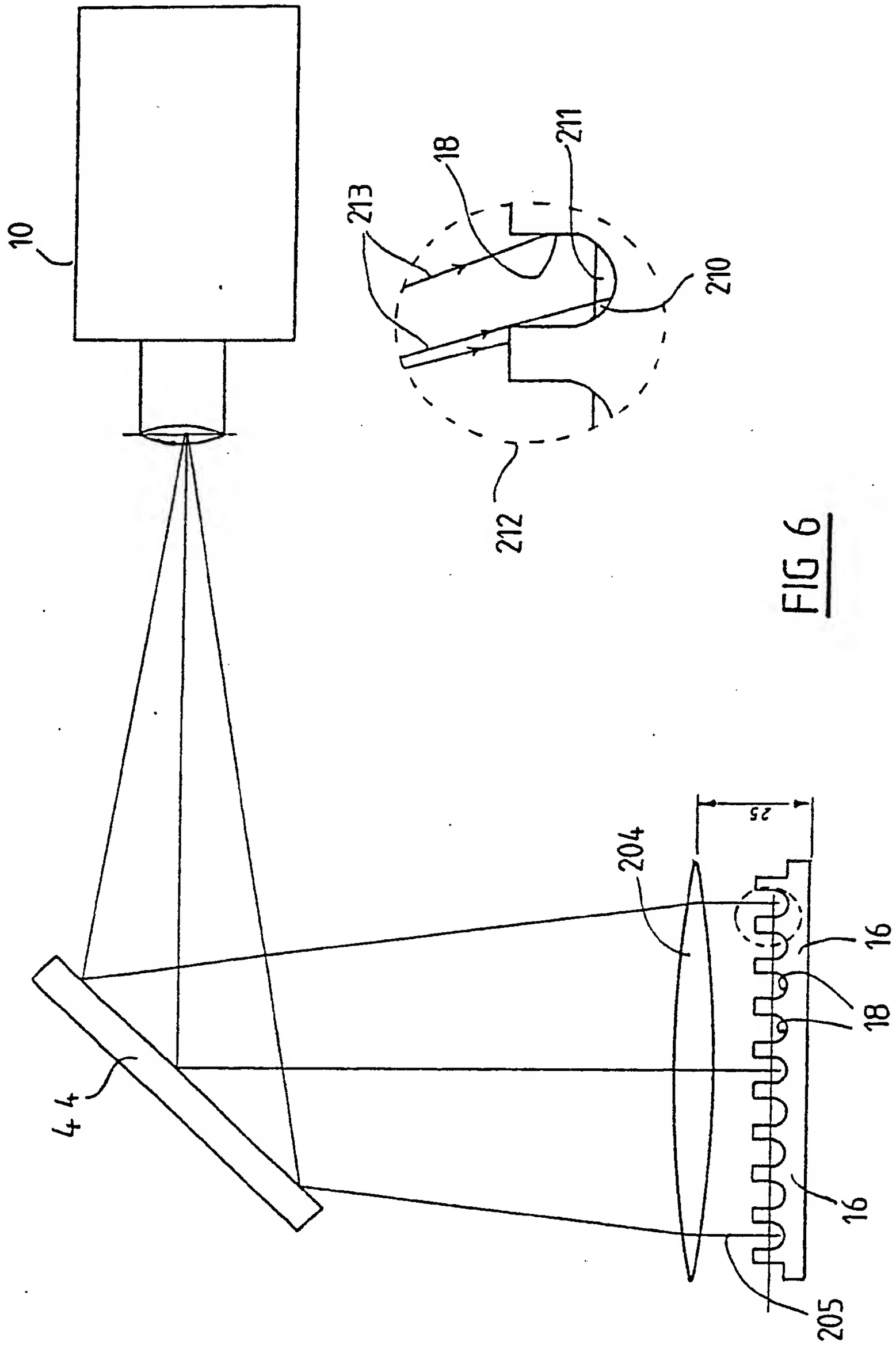

FIG 6

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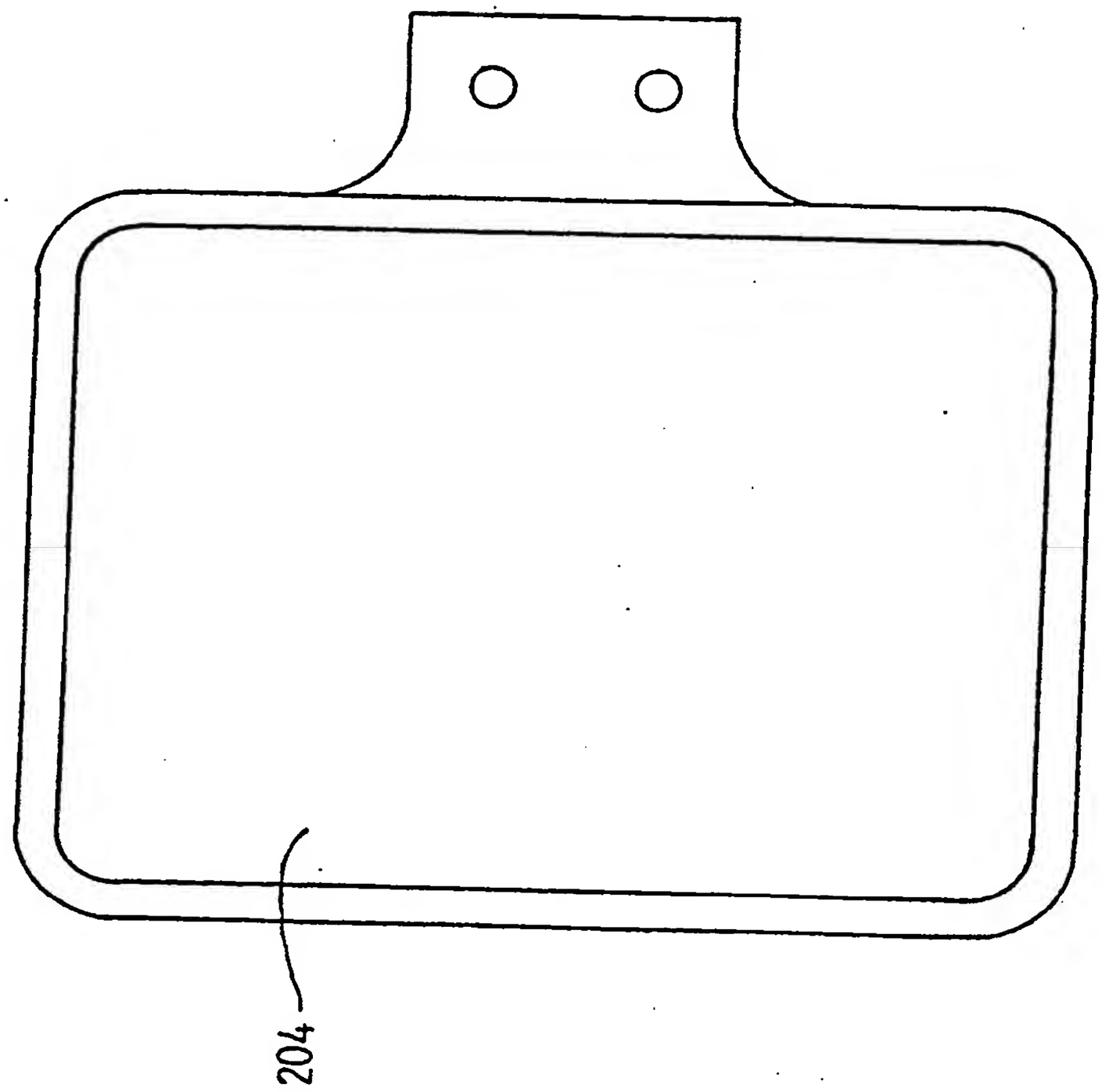
FIGURE 7



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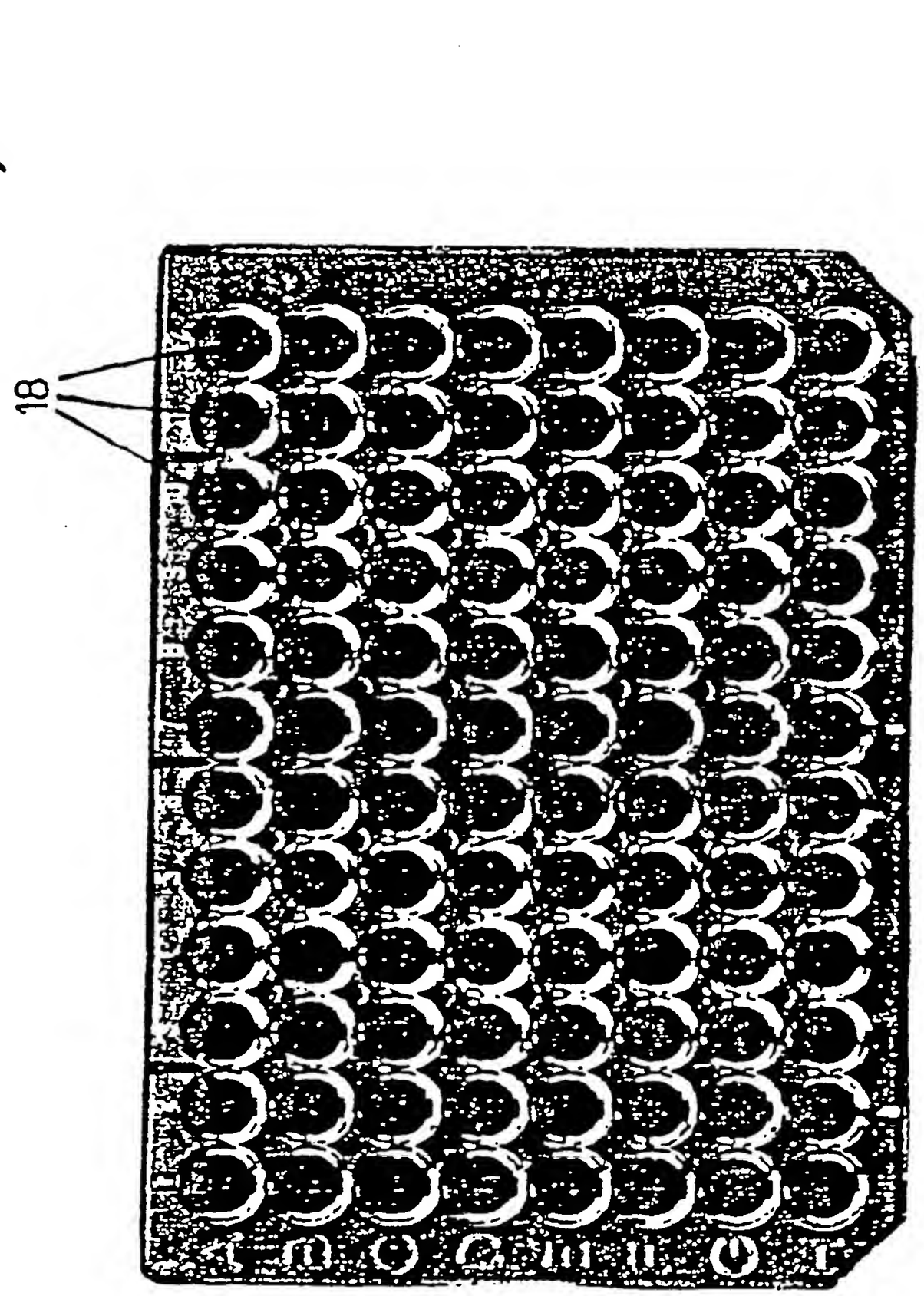

FIGURE 8

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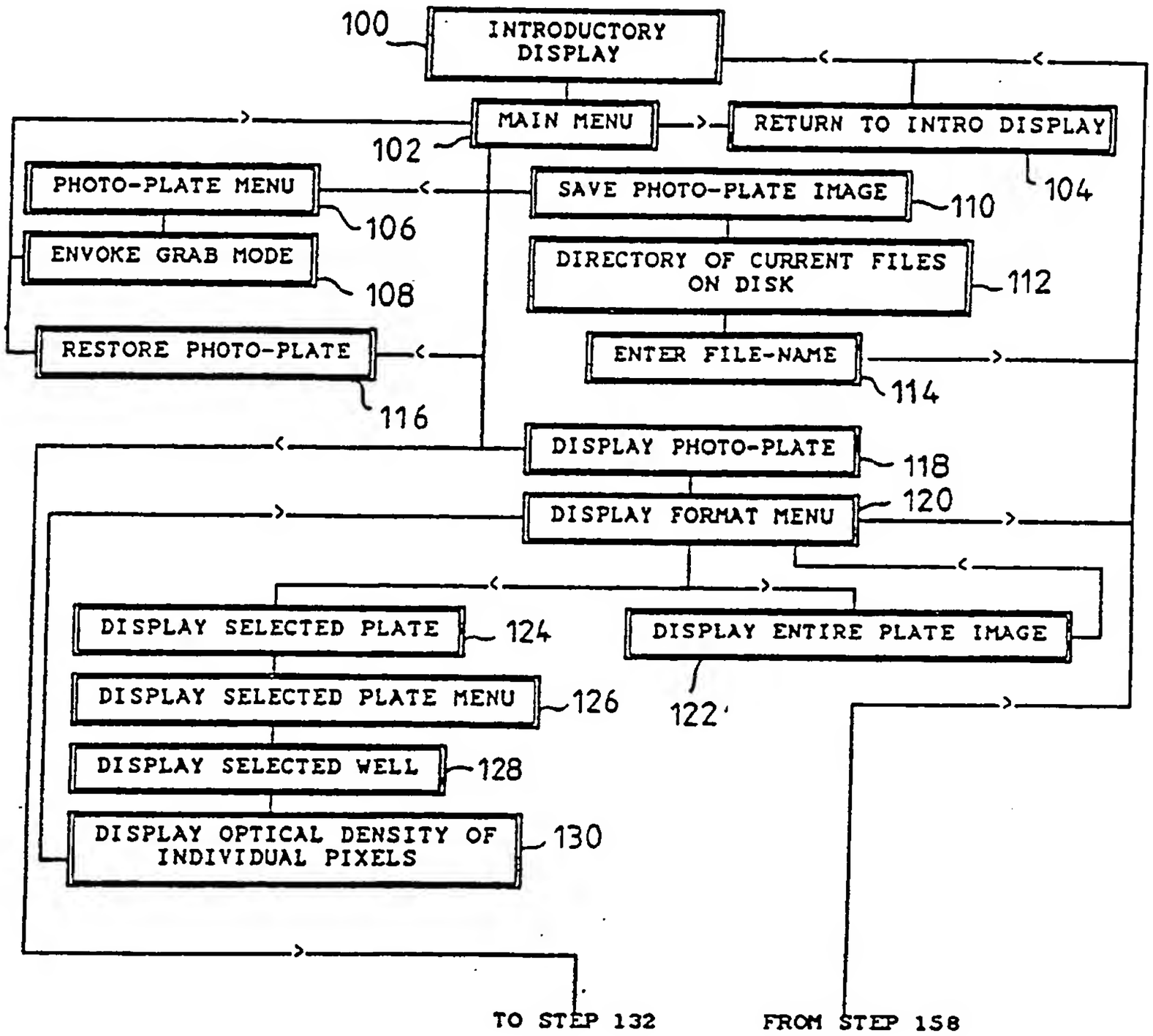

FIGURE 9

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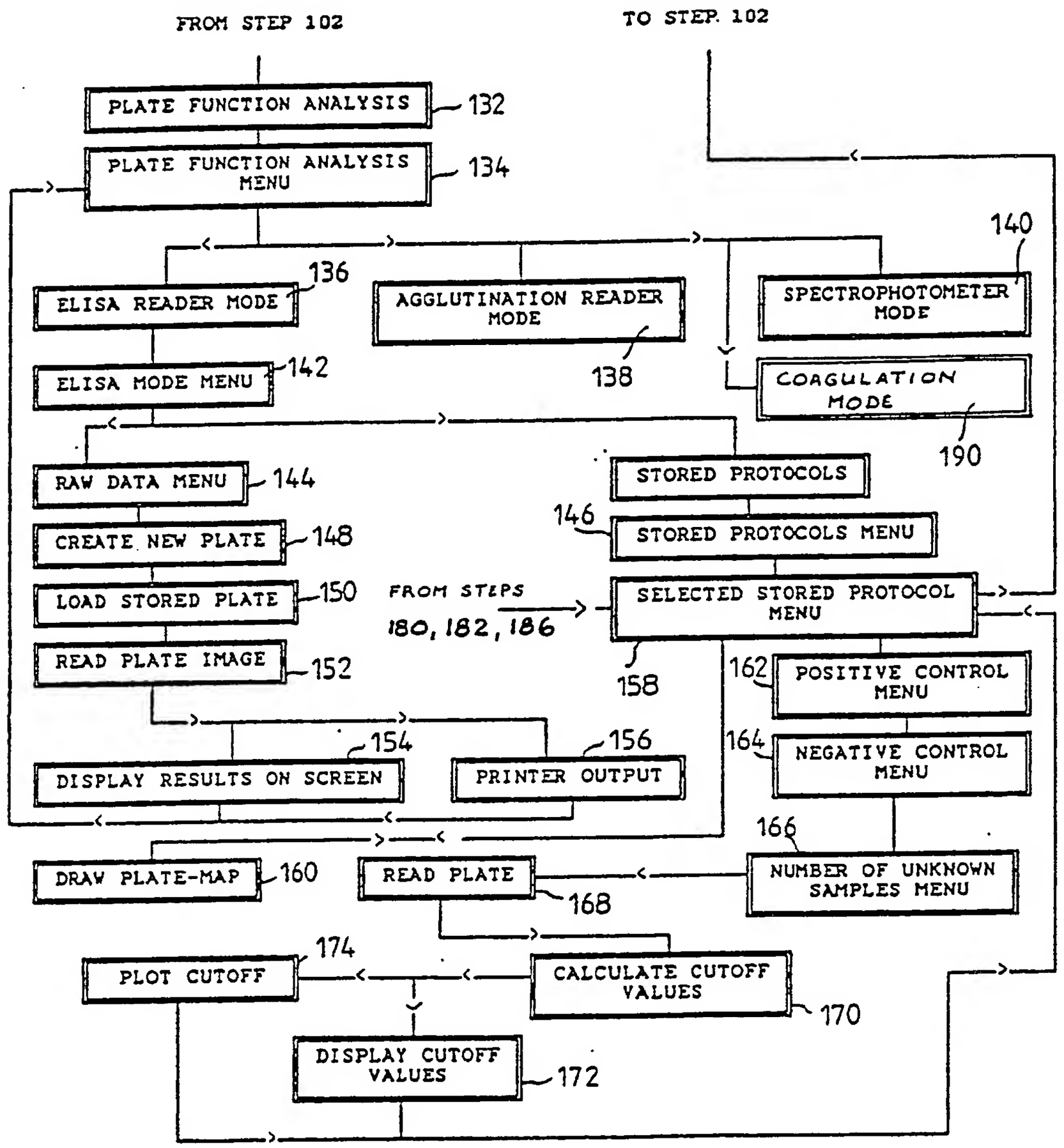

FIGURE 10

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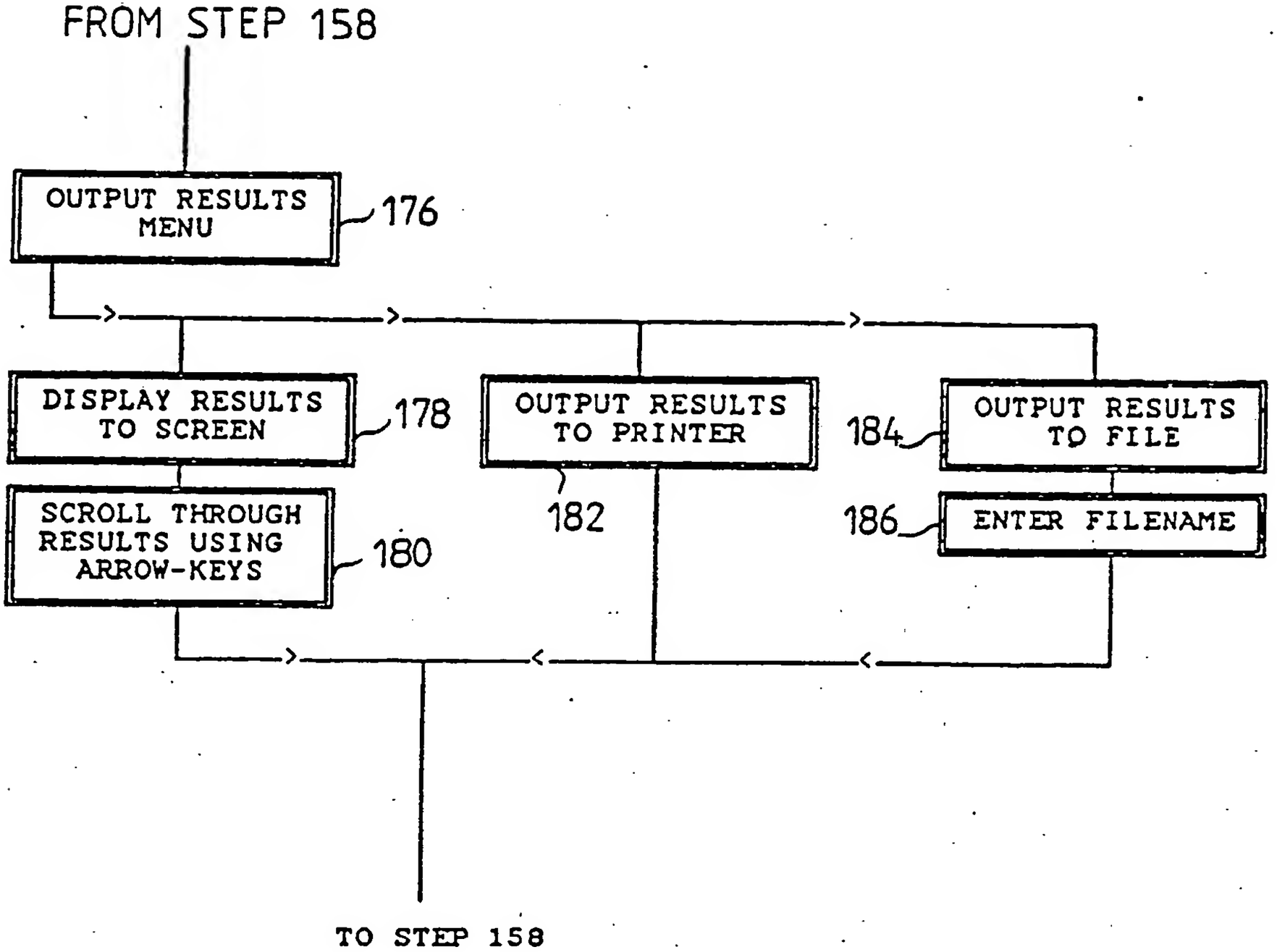

FIGURE 11

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FIGURE 12

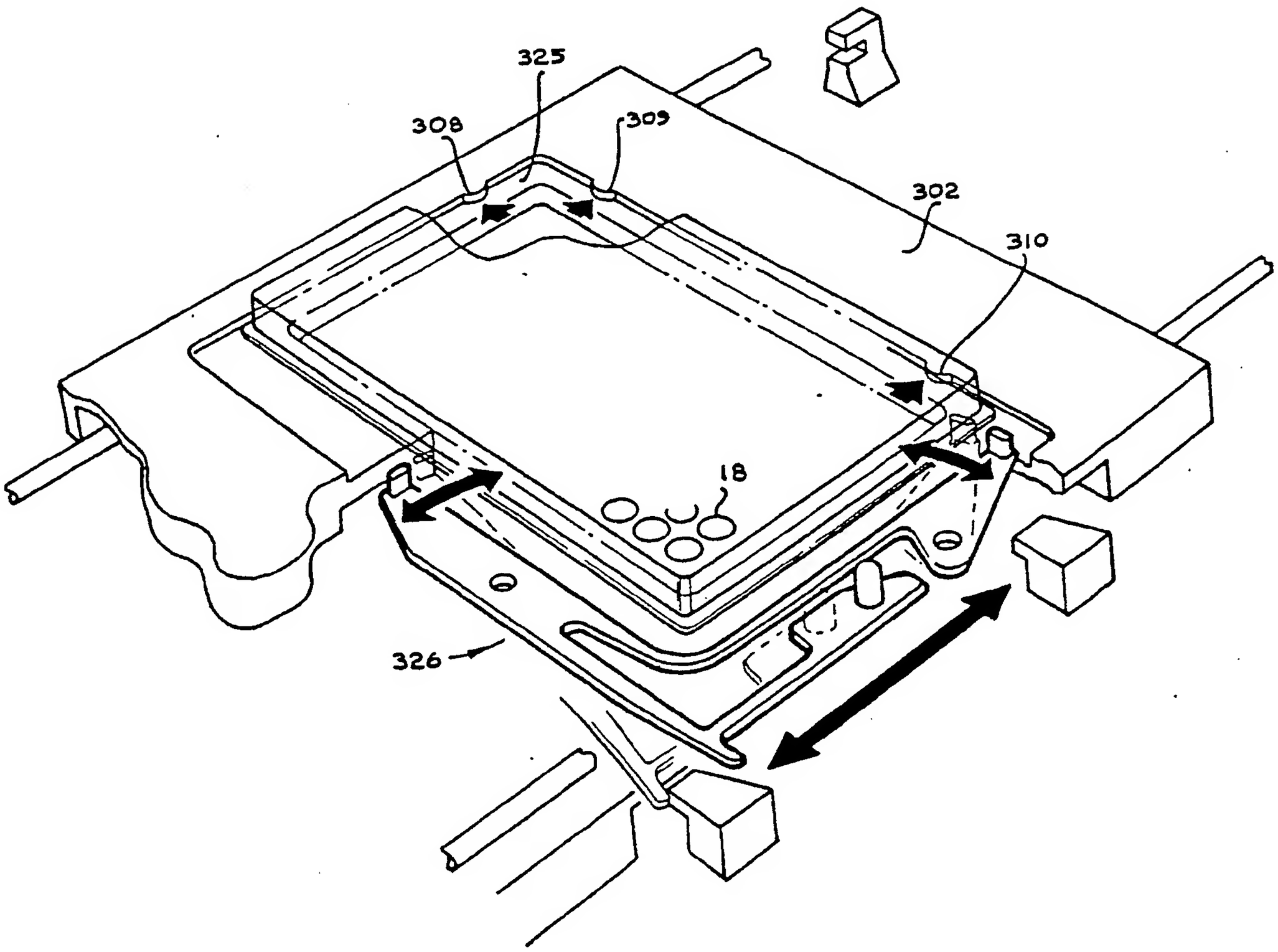

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FIGURE 13A

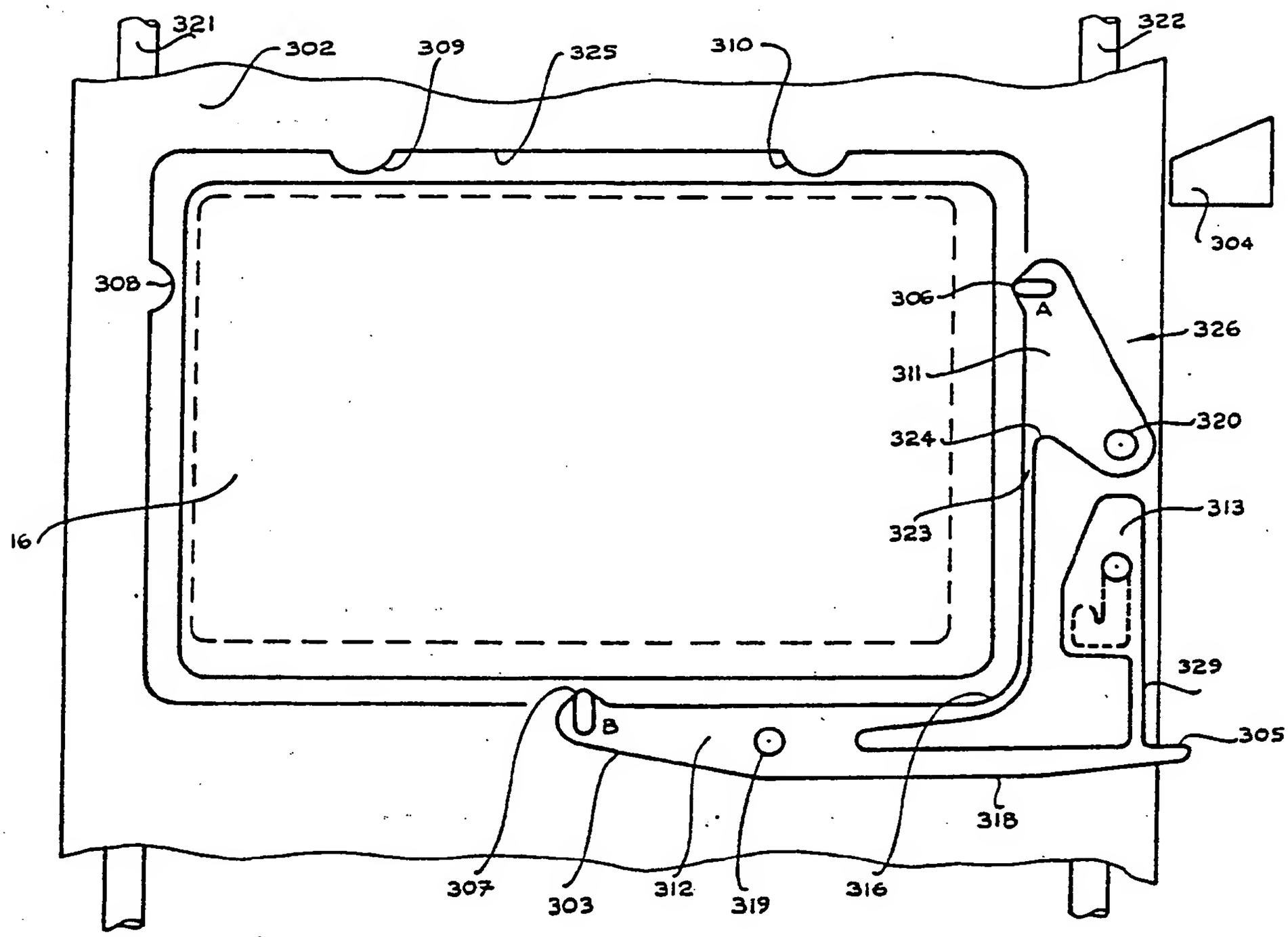

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FIGURE 13B

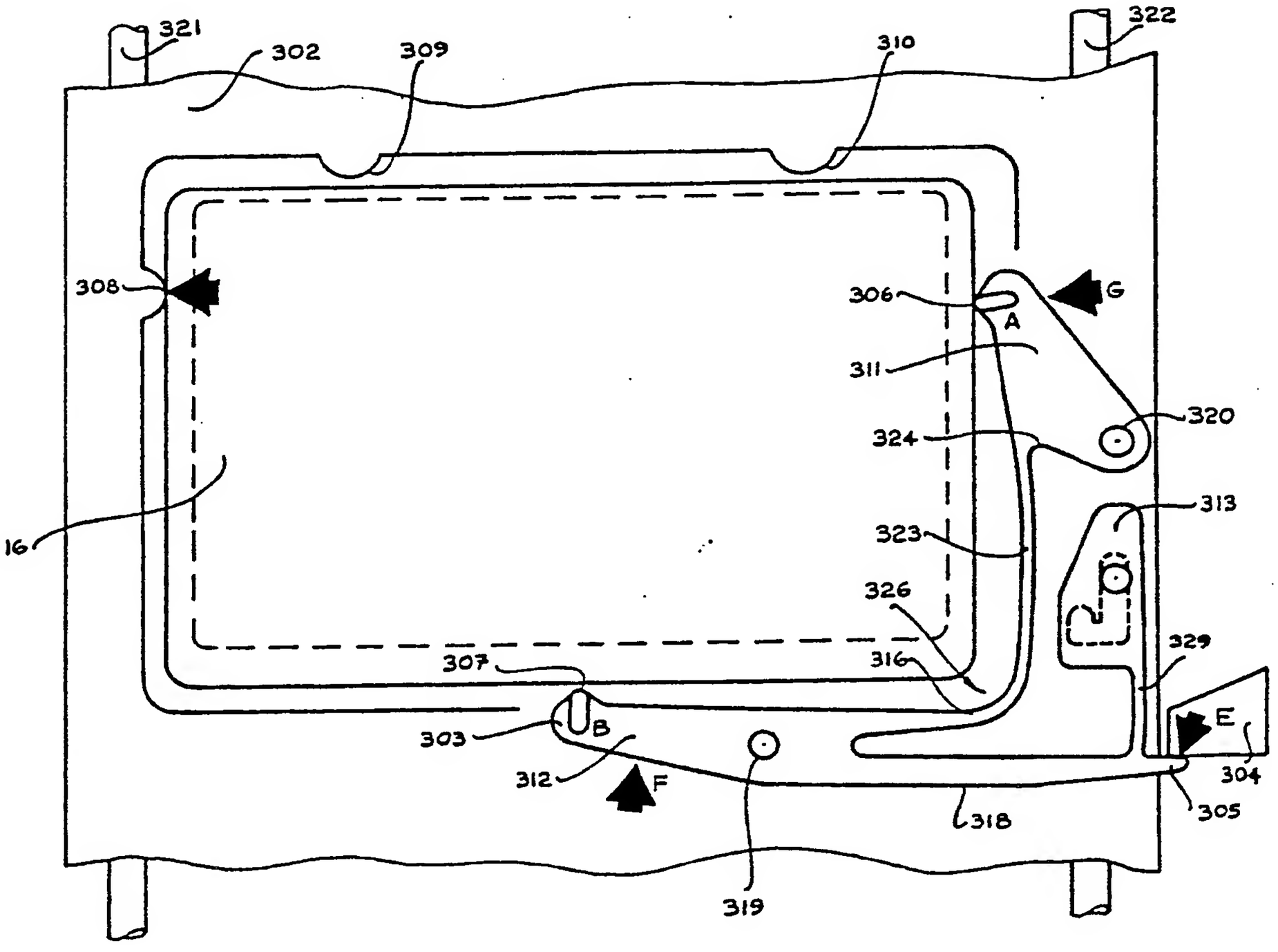

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FIGURE 13C

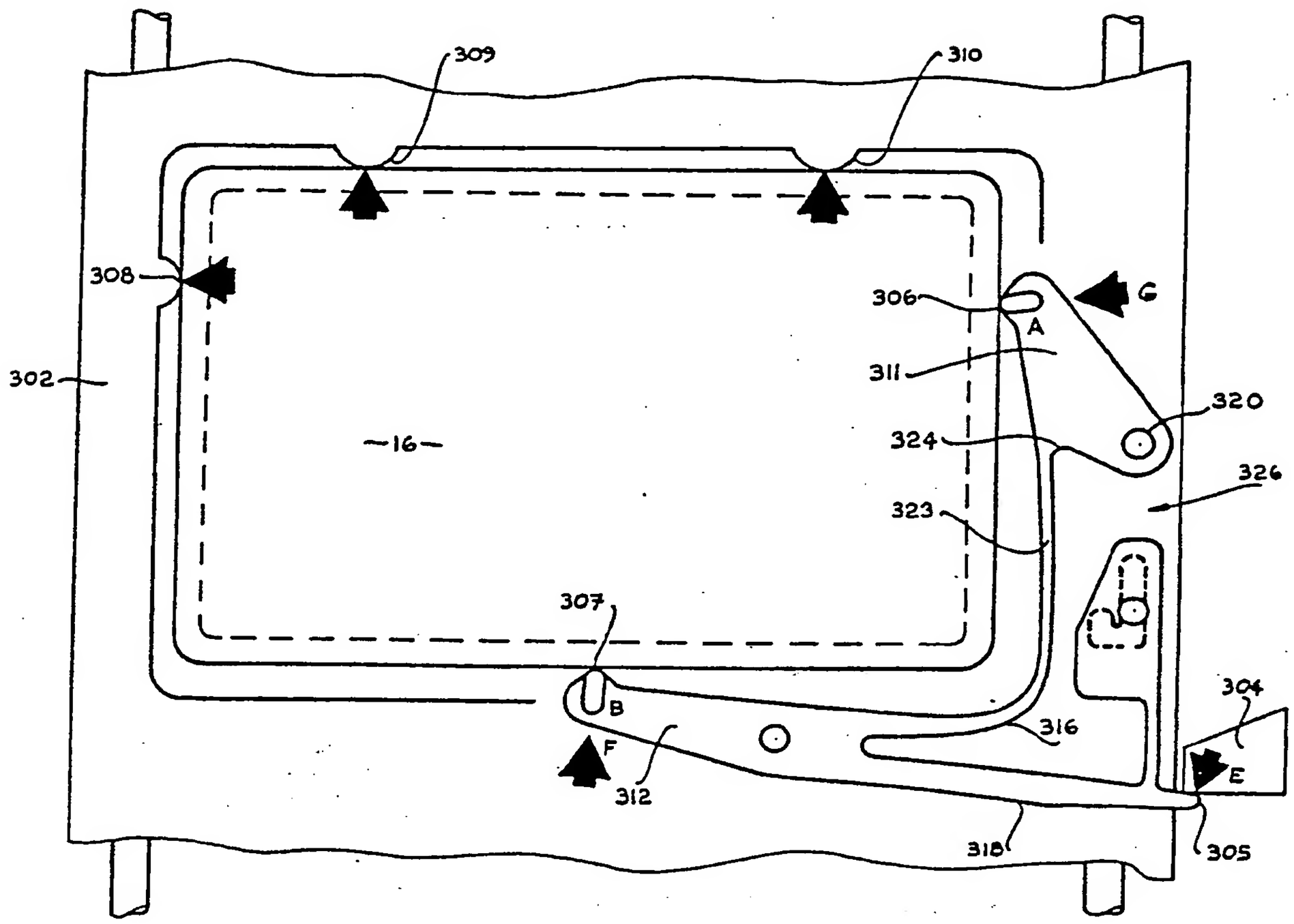

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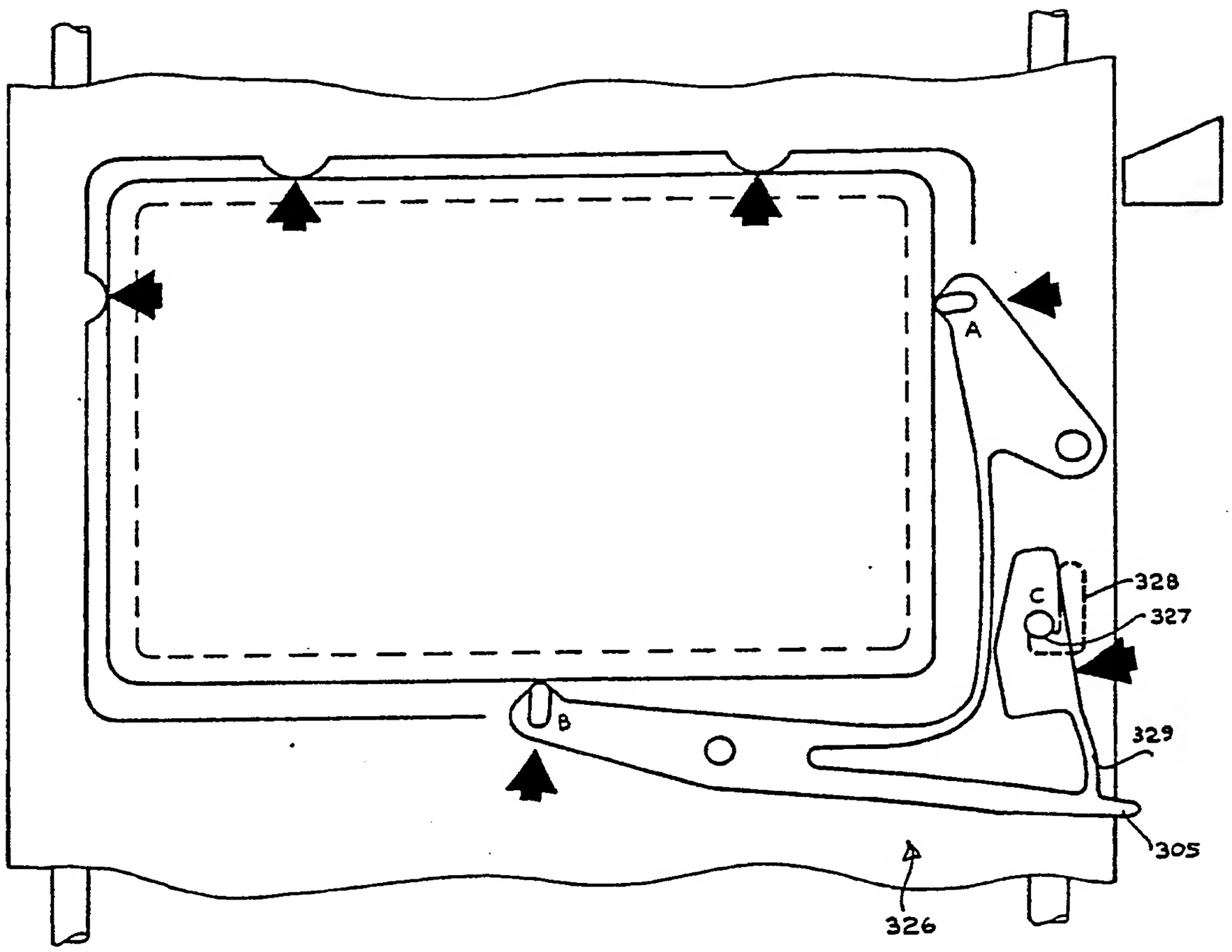
FIGURE 14



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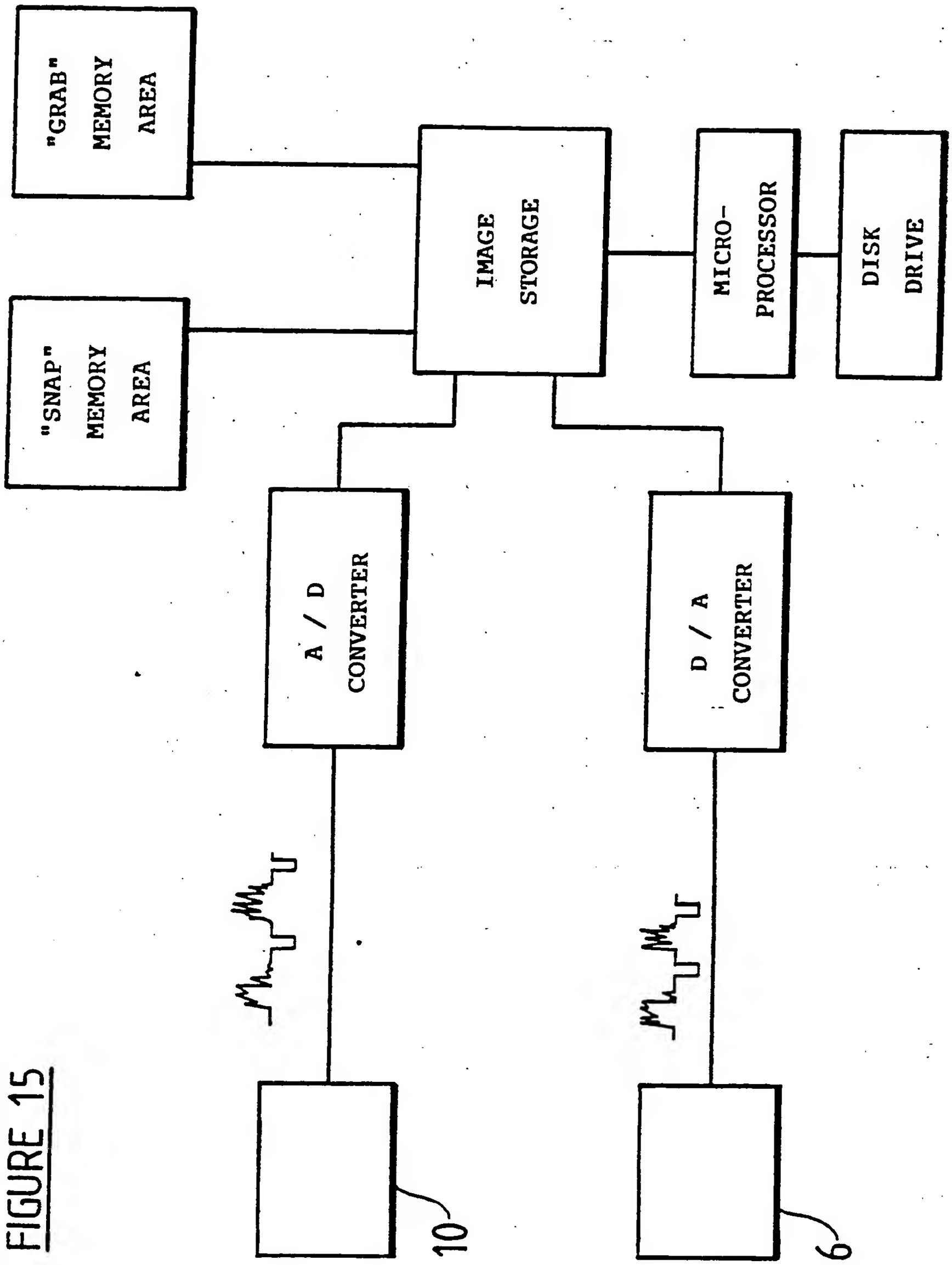

FIGURE 15

BNSDOCID: <WO___9002326A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 89/00312

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[4] G01N 21/90, H04N 7/18, G12B 5/00, B23Q 16/02

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	H04N 7/18, G01N 21/90, G12B 5/00, B23Q 16/02

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

AU:IPC as above plus G12B 9/00, 9/10, G01N 35/00, F16M 11/00, 11/02, 11/04, B23Q 17/04 (IPC3)

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X,Y	US,A, 4245243 (Gutjahr) 13 January 1981 (13-01-81)	1,2,9-11,13,15,16
X,P,Y	Patent Abstracts of Japan P-13, page 104 JP,A,63-259465 (HITACHI LTD.) 26 October 1988 (26.10.88)	1,9-11,13,15,16
X,Y	Patent Abstracts of Japan P-12, page 42 JP,A,62-247250 (HITACHI ELECTRONICS ENG. CO. LTD.) 28 October 1987 (28.10.87)	1,13,9-11,15,16
Y	GB,A,2057220 (The Secretary of State for Defence, Whitehall) 25 March 1981 (25.03.81)	9,10,11,16
Y	AU,B,80635/82 (548239) (KIRIN BEER K.K.) 26 August 1982 (26.08.82)	9,13
Y	US,A,3947628 (Alien) 30 March 1976 (30.03.76)	15
Y	GB,B,1499888 (PHILIPS ELECTRONIC and ASSOCIATED INDUSTRIES LTD) 1 February 1978 (01.02.78)	16

(continued....)

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 October 1989 (10.10.89)	17 October 1989
International Searching Authority	Signature of Authorized Officer
Australian Patent Office	R. MURRAY

Form PCT/ISA/210 (second sheet) (January 1985)

BNSDOCID: <WO___9002326A1_I_>

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US,A,4509081 (PEYTON) 2 April 1985 (02.04.85)	
A	AU,B,86353/82 (550122) (KIRIN BEER K.K.) 3 February 1983 (03.02.83)	
A	US,A,4126376 (Gommel) 21 November 1978 (21.11.78)	
A	DE,A,3803031 (DIGITAL ELECTRONIC AUTOMATION S.p.A.) 11 August 1988 (11.08.88)	

V. [] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[] Claim numbers , because they relate to subject matter not required to be searched by this Authority, namely:

2.[] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[] Claim numbers , because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [X] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

Claims 1-16, 24 and

Claims 17-23

1.[X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.[]No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[] The additional search fees were accompanied by applicant's protest.

[X] No protest accompanied the payment of additional search fees.

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